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## OBSERVATIONS ON THE ORIGIN AND STATUS OF THE SO-CALLED "TRANSITIONAL" WHITE BLOOD CELL<sup>†</sup>

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Probably the status of no white cell of the blood is so uncertain as that of the so-called transitional cell. The original hypothesis of Ehrlich<sup>1</sup> that this cell was a transition form between the large mononuclear and the polymorphonuclear has long since been discarded, although Sahl<sup>2</sup> still adheres to the view that it is an intermediate stage between the myelocyte and the polymorphonuclear neutrophil. By many (Ehrlich,<sup>3</sup> Emerson, Webster and Simon, in the latest editions of their text-books) it is believed to be a senile form of the large mononuclear. Pappenheim and Naegeli<sup>4</sup> refute the hypothesis that this cell is a transitional form between the large mononuclear and the true polymorphonuclear neutrophil, the former regarding it as a pro-myelocyte in his scheme of blood-cell origin, while Naegeli, after first describing it as related to the myeloblast<sup>4</sup> concludes that, together with the other mononuclears, exclusive, of course, of those of known origin such as the large lymphocyte, it forms an independent cell type of myeloid origin.<sup>5</sup> As an independent cell type it has also been assigned to the lymphoid system, as coming (1) from the "*Kernzentrumzellen*" (Weidenreich, Pappenheim in his earlier studies, et al)<sup>6</sup> and (2) from the spleen-pulp and marrow-cord cells of the lymph nodes

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<sup>†</sup> Submitted for publication Aug 25, 1915

\* From the Medical Clinic of The Johns Hopkins Hospital

1 Ehrlich, P. *Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes*, p 126, Berlin, 1891, A. Hirschwald

2 Sahl, H. *Lehrbuch der Klinischen-Untersuchungs-Methoden*, p 894, Ed 5, Leipzig and Vienna, 1909, Franz Deuticke

3 Ehrlich, P., and Lazarus, A. *Anemia*, Nothnagel's Practice of Medicine, Am. Ed., 1905, viii, 66

4 Naegeli, O. *Anaemia*, Lazarus, A., and Naegeli, O., p 95, Ed 2, New York, 1910, Rebman & Co

5 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, p 186, Leipzig, 1912, Veit & Co

6 Quoted by Naegeli, Note 5

(Meyer-Heineke, Gruber, Turk)<sup>6</sup> It has also been considered an adventitia cell (Sternberg)<sup>6</sup> and of endothelial origin (Marchard,<sup>6</sup> Mallory,<sup>7</sup> Adami and McCrae<sup>8</sup>), and Warfield<sup>9</sup> is so convinced of such an origin for the cell that he suggests the name endotheliocyte Bunting,<sup>10</sup> recently asserting that it does not come from the endothelium lining lymph spaces, maintains that he has adduced proof of its origin in the germinal centers of the lymph glands Cabot<sup>11</sup> speaks indefinitely of all large mononuclears as arising, some from the bone marrow and others from the endothelium, and Turk<sup>12</sup> in his latest expression of opinion agrees with Naegeli that the large mononuclear leukocyte is of myeloid origin It is with the hope of shedding some light on this obscure subject that the following observations, concerning an unusual transitional cell reaction after the administration of salvarsan, are reported

#### CASE REPORT

*History*—S W (Genl No 100573) East Indian, aged 29, was admitted to The Johns Hopkins Hospital, Feb 5, 1915, complaining of shortness of breath

His past history was of no importance, except that he denied lues but admitted a gonorrheal infection eight months previously which was followed by a swelling of the testicles for a short time

The present illness began about six weeks before admission, with shortness of breath on ordinary exertion, this had persisted without any increase in intensity and was the only symptom of which the patient complained

*Examination*—The physical examination on admission showed a blotchy, mahogany-colored pigmentation over the arms, legs, body and back, greatly resembling a healing secondary luetic rash The axillary and epitrochlear glands were palpable, but small and soft The heart was enlarged the point of maximum impulse being best seen outside the nipple line, and the left border of relative cardiac dulness lying 2 cm outside this line There was a soft to-and-fro murmur over the apex, the systolic being softly transmitted to the axilla, and a to-and-fro murmur at the base, the diastolic well transmitted down the left sternal margin Retromammary dulness was 8 cm wide The pulse was collapsing in quality There was no arterial thickening Liver dulness reached the costal margin in the midclavicular line The spleen was not palpable and the area of splenic dulness was not enlarged There was a typical scar of a chancre on the dorsal prepuce, and the lower pole of the left epididymis was enlarged The eyegrounds were negative Massage of the prostate produced a few drops of cloudy material in which no gram-negative cocci could be demonstrated His temperature was 97.8, pulse 80, respirations 24, blood pressure 110/75 (Tycos)

<sup>7</sup> Mallory, F B Pathologic Histology, Ed 2, p 23

<sup>8</sup> Adami and McCrae Textbook of Pathology, Ed 2, p 446, Philadelphia 1914, Lea & Febiger

<sup>9</sup> Warfield, L M The Normal Differential Leukocyte Count, Jour Am Med Assn, 1915, lxiv, 1296

<sup>10</sup> Bunting, C H The Blood-Picture in Hodgkin's Disease, Bull Johns Hopkins Hosp, 1911, xxii, 369, 1914, xxv, 173

<sup>11</sup> Cabot, R C The General Pathology of the Blood-Forming Organs, Modern Med, Osler and McCrae iv, 610

<sup>12</sup> Turk, W Vorlesungen über klinische Haematologie, Part 2, p 143, Vienna and Leipzig, 1912 Wilhelm Braumüller

*Blood Examination*—Fresh blood, normal in appearance Red blood cells, 4,720,000, white blood cells, 9,000, hemoglobin 101 per cent (Sahli)

Differential Polymorphonuclear neutrophils, 61.8 per cent, polymorphonuclear eosinophils, 0.25 per cent, polymorphonuclear basophils, 0.25 per cent, lymphocytes, 28.6 per cent, large mononuclears, 8.4 per cent, transitionals, 0.8 per cent

Urine Light color, turbid, specific gravity 1.012, acid, no sugar, faint trace of albumin, a few hyaline casts and pus cells

Stool negative

Impression on Admission Luetic aortitis with aortic regurgitation, moderate hypertrophy of the heart

February 5 Mercurial ointment, 1 dr, asunction, q n, and potassium iodid, grs xv, t i d, begun

February 9 Wassermann test positive

February 10 Mercurial ointment, 1 dr, asunction, q n discontinued Salvarsan, 0.3 gm, in freshly distilled water administered intravenously, no reaction

February 15 Salvarsan, 0.45 gm, in freshly distilled water administered intravenously Six hours after administration the patient's temperature began to rise reaching 104 in a few hours, he had a severe chill and then general malaise for four or five hours Except for a pronounced tachycardia, there was no focal reaction of the aorta made out, and there were no anginal attacks

February 16 Condition at the end of twenty-four hours about the same Potassium iodid discontinued Blood count red blood cells, 5,144,000, white blood cells, 7,840, hemoglobin 91 per cent (Sahli)

February 17—Daily examination of urine showed a specific gravity of from 1.011 to 1.027, a constant slight trace of albumin, and except on day of admission there was no casts noted

Roentgen Ray Report Aorta dilated and heart enlarged

February 18 Diffuse scarlatiniform rash noted over face and body

February 19 Muscles of legs tender to lightest palpation Urine decreased in amount, albumin more abundant and many granular casts present Blood total non-protein nitrogen, 44 mg, urea nitrogen, 27 mg, Ambard's constant, 0.22

February 20 Legs still tender, now swollen There was, however, no other evidence of thrombosis Temperature falling

February 22 Temperature normal Phenolsulphonephthalein excretion after 1½ hours, 34 per cent, after 2½ hours, 35 per cent, total for the four hours, 69 per cent

February 26 Lower extremities showed very little tenderness and no swelling Sclerae definitely jaundiced Liver edge about 3 cm below costal margin in the right midclavicular line Spleen not palpated and area of splenic dulness not enlarged Red blood cells 5,600,000, hemoglobin 85 per cent (Sahli)

March 2 Temperature rose to 102 on the previous evening, and remained at this point Patient quite deeply jaundiced and liver edge 6 cm below the costal margin in the right midclavicular line Left lower leg slightly swollen, showed increased resistance to palpation over belly of tibialis anticus and extensor hallucis longus muscles, and there was marked limitation of dorsoflexion of the great toe

From February 19 the urine varied in specific gravity from 1.006 to 1.019, the quantity of albumin and the number of casts decreased and there was no blood Bile had been present constantly since February 21

Blood Total nonprotein nitrogen, 20 mg, urea nitrogen, 10 mg

March 3 Jaundice still quite marked One slight epistaxis on this date

March 7 Some oozing of blood from gums noted Spleen still not enlarged. Red blood cells, 3,705,000, hemoglobin, 80 per cent (Sahli)



March 8 Temperature, after running a remittent course since March 2, reached normal. Precordial pain complained of and pericardial friction made out. Stool colorless, showing much fatty acid and fat, gave negative test for bile.

March 16 Signs of effusion in pericardial and both pleural cavities made out. Pericardial friction not noticed since March 15. Roentgen ray report of chest: Huge triangular heart shadow, probably pericardial effusion.

March 18 Stool gave positive test for bile. No discomfort complained of, but pleural and pericardial effusions present, though not so extensive as previously noted. Urine still showed albumin, a few granular casts and bile.

April 9 Temperature normal and patient feeling very well. Still deeply jaundiced and looking quite weak. There were no signs of pericardial or pleural effusion. The heart was enlarged, relative cardiac dullness extending 3 cm. to the right of mid-sternal line, and to the left as far as the anterior axillary line. The murmurs were practically the same as noted on admission. Retromammary dullness 10 cm. wide at level of first intercostal space. Liver edge  $1\frac{1}{2}$  cm. below costal margin in right mid-clavicular line. Spleen not palpated and area of splenic dullness not enlarged. There was no edema, tenderness or paralysis of the lower extremities. Urine still showed a trace of albumin and a few granular casts. The blood pressure during the patient's stay in the hospital varied between 110 and 125 systolic. Patient insisted on leaving the hospital, and was discharged against advice.

May 30 Returned to the dispensary to be treated for the jaundice, which still persisted to a slight degree. Had been working and felt quite well.

In addition to the findings above noted the reaction of this patient was manifested by unusual changes in the white blood cell picture as may be seen by reference to the table of total and differential leukocyte counts. Except for an acute polymorphonuclear leukocytosis accompanying the pericarditis, the changes were almost entirely in the percentage of the true so-called transitional cells described below. The differential counts recorded in the table were made on smears stained by the Romanowski method (Wilson's modification) and these were checked in each instance by counts on smears made at the same time and stained with Ehrlich stain.

#### DESCRIPTION OF CELLS CONCERNED IN THE REACTION

Those cells classified as transitionals (Fig. 1) in the differential counts in this case were always as large as, and generally larger than, the polymorphonuclears, and varied in diameter from 10 to 20 microns. The nucleus in each cell was irregular and in most of them typically indented or saddle-bag shaped, the protoplasm was abundant and the cell boundaries sharp and even. Stained by the Romanowski method (Wilson's modification) the nucleus appeared rather densely reticulated and of a dark purple color. The protoplasm was a pale blue and quite thickly set with an apparent fine neutrophilic granulation much resembling that seen in the polymorphonuclear neutrophil, and occasionally seeming to overlie the nucleus. In a few cells large azure granules suggesting those encountered in the protoplasm of the large mononuclears were also present. Stained with Ehrlich's stain

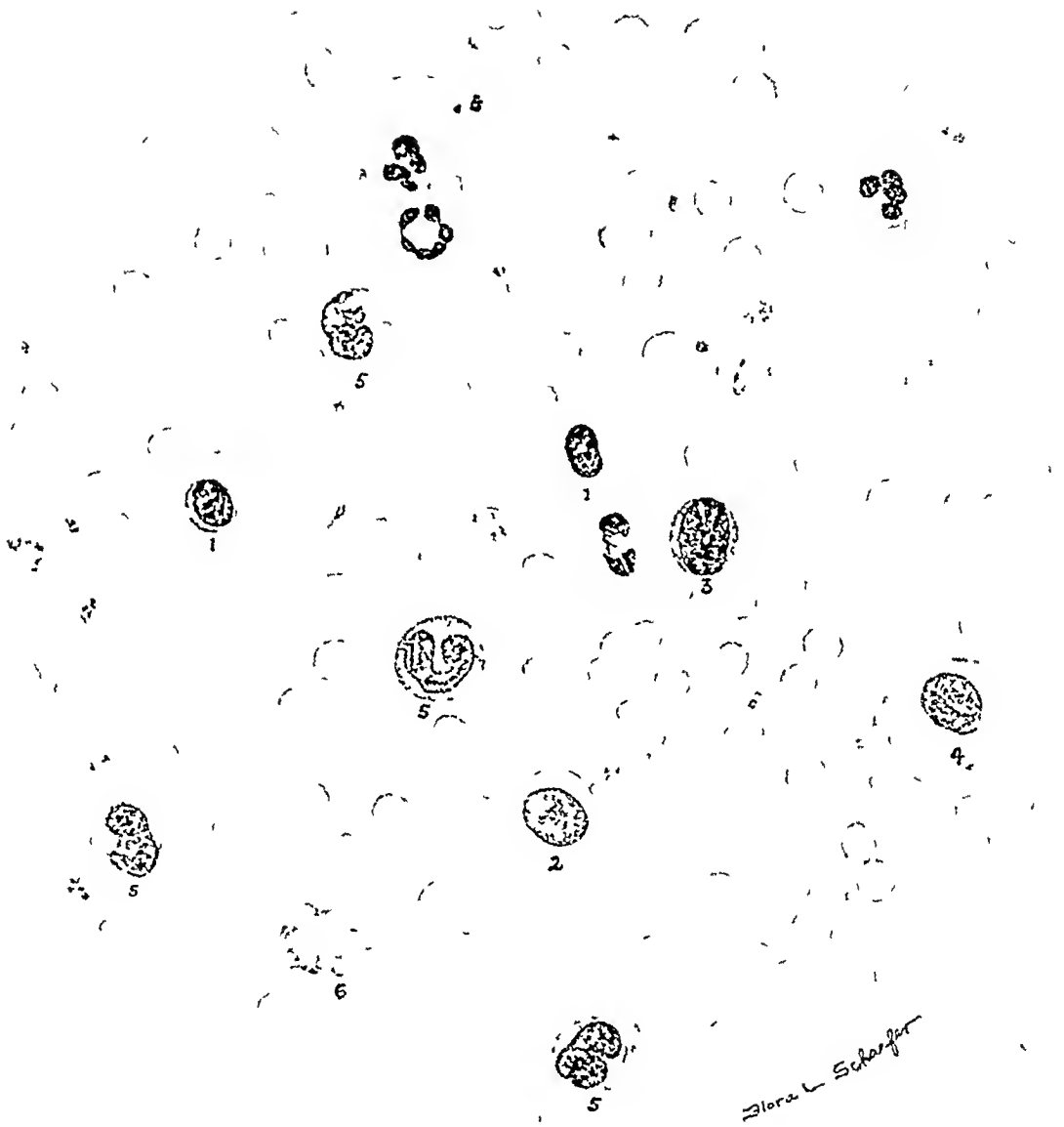


Fig 1—Field taken from smear made March 16 and stained with Wilson's stain, showing some types of cells encountered and illustrating their classification. The evidence of mild secondary anemia present in this field represents fairly accurately the true condition at this time. 1 Small lymphocyte. 2 Large lymphocyte. 3 Large mononuclear quite different from the transitional. 4 Large mononuclear closely resembling the transitional. 5 Transitional. 6 Degenerated cell—unclassified. Although 4 definitely and 3 quite probably belong to the transitional cell group, both were included with 2 and classed as large mononuclears.



TABLE OF TOTAL AND DIFFERENTIAL WHITE BLOOD CELL COUNTS

Date	W B C	P M N	P M B	P M E	Lymph	L M	Myeloc	Trans	Unclass
Feb 5	9,000	618	025	025	286	84		08	
Feb 10*								..	
Feb 15†									
Feb 26	6,700	380	16		136	84		400	52
March 4		72			228	88		544	16
March 7	7,180	216	12		124	84		548	
March 8‡									
March 11	13,280	630			40	50	40	200	40
March 12	18,280	604			24	80	20	272	
March 15†									
March 16	22,600	680			20	70		160	70
March 18	21,600	300			20	30		110	540
March 21	11,300	740		10	80	20		130	20
March 23	8,040	560			40	100		150	150
March 25	6,100	524	40	24	132	72	04	168	72
March 27	7,200	520	12	52	144	60	08	160	44
March 29	7,900	550		64	50	100		190	110
April 1	7,600	532	08	02	148	140		84	24
April 3	8,440	532	04		116	180		48	100

\* 0.3 gm salvarsan intravenously

† 0.45 gm salvarsan intravenously

‡ Pericardial friction heard

e nucleus was a greenish-blue, showing no evidence of reticulation, and the protoplasm a faint pink with a very fine, indistinct, dust-like granulation of pinkish hue. The granulation which was so definite with Wilson's stain, was either absent with this stain or represented by a few faint pink granules which were never seen to overlie the nucleus. With Jenner's stain the protoplasm was a darker blue than with Wilson's, and the granulation, though constantly present, was not so striking. In none of these cells was a perinuclear clear zone noted. Using the "indophenolblau" reaction of Schultze,<sup>13</sup> oxydase granules were demonstrated in these cells in just as great abundance as in the polymorphonuclears. By means of staining the nucleus with saturated aqueous safranin before submitting the smears to the oxydase reaction, the different cells were definitely identified, although owing to the occasional overlying of the nucleus with oxydase granules the differential diagnosis between the transitionals and the polymorphonuclears was difficult in some instances.<sup>14</sup>

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13 Schultze, W. Zur Differentialdiagnose der Leukamien, *München med. Wehnschr.*, 1909, lvi, 167. See also Turk (Note 12), p. 202.

14 It was at first hoped that by staining the nucleus in connection with the oxydase reaction, a preparation might result that would admit of a microphotograph and thus make a permanent demonstration of transitional cells containing oxydase granules. The blue nuclear stains were of no help. Aqueous safranin, gentian-violet and cochineal were also tried, and of these safranin proved the most satisfactory, giving the desired intensity of staining in the shortest time. To save the oxydases from destruction, aqueous solutions used without a mordant were necessary, and under these conditions it required about eight minutes, depending somewhat on the age of the smear, to get a satisfactory staining of the nucleus with the saturated solution. Being an aqueous stain, it was rapidly dissolved out by the water in the dimethylparaphenyldiamin and alphanaphthol solutions used in the "indophenolblau" synthesis, so that when these solutions were allowed to remain on the smear long enough to result in a preparation of any permanency the red stain of the nucleus had become too faint to be photographed. On the other hand, if the smears were submitted to the oxydase reaction first, the eight minutes consumed in staining the nucleus rendered the preparation unsatisfactory by reason of the transient character of the oxydase reaction, which endured only about ten minutes. The technique finally adopted was as follows:

(a) Staining

- 1 Fix smears eight hours in formaldehyd vapor
- 2 Stain in saturated aqueous safranin solution for eight minutes
- 3 Wash quickly in water and dry immediately by careful blotting

(b) Oxydase reaction. Put on slide

- 1 One drop of 1 per cent aqueous solution of dimethylparaphenyldiamin, and
- 2 One drop of freshly prepared 1 per cent solution of alphanaphthol in 1 per cent KOH dissolved by gentle heating
- 3 Mount previously stained smear in this and examine at once

By this means a preparation of sufficient permanency of both the nuclear stain and oxydase granules was obtained to admit of satisfactory identification of the cells and a hasty differential count, but not enduring long enough to be photographed.

In order that any conclusions drawn from this case might be justified, strict adherence to the above characteristics was demanded of any cell counted with the transitionals. Any cell resembling a transitional to some extent but having a ground or oval nucleus, or having a somewhat irregular nucleus but lacking the customary intensity of granular staining with Wilson's stain, was classed with the large

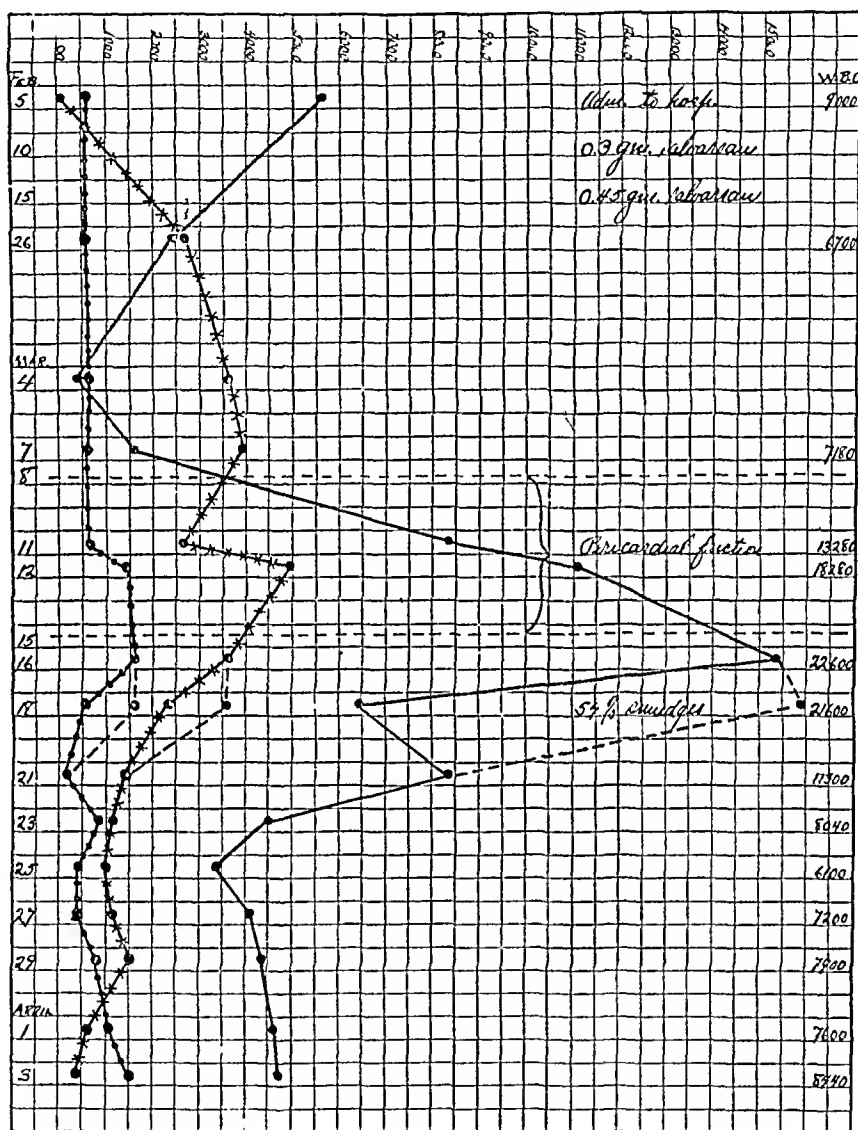


Fig 2—Curves of the polymorphonuclears, transitionals and large mononuclears in absolute number of cells per cubic millimeter of blood. The dotted lines represent the curves after the 54 per cent unclassified cells noted March 18 had been proportionately allotted to each. Solid line above polymorphonuclears, line with dots, transitionals, line with crosses, large mononuclears.

mononuclears. Never, however, was a cell having a typically indented nucleus encountered which did not meet the qualifications in regard to granular staining, nor was a cell with the characteristic granules ever seen with a perfectly round or oval nucleus. The classification of those cells counted as lymphocytes, although not based on the size of the cell, was equally strict, only those with a deep blue-black

nucleus with Wilson's stain and a faint greenish-blue with Ehrlich's, and having a narrow strip of protoplasm, being counted in this group. The cells commonly accepted as large lymphocytes with a purple reticulated nucleus and abundant faint blue protoplasm, clear except for occasional azure granules with Wilson's stain, and a very faintly staining blue nucleus and pink protoplasm with Ehrlich's, and with a fairly constant perinuclear clear zone, were, together with the cells above described somewhat resembling the transitionals, included with the large mononuclears. Thus the group of large mononuclears was a composite one made up of at least two distinct types of cells, those resembling the transitionals preponderating. There was no transition stage between the true large lymphocyte and the cells resembling the transitionals but not exactly typical of them, although among these latter there were all gradations in point of intensity of granulation and shape of nucleus, from the most atypical to the true transitional. With Wilson's stain the more reticulated and irregular nucleus of the transitional, the neutrophilic granulations of its protoplasm and uniformly sharp edge, and the absence of the perinuclear clear zone, rendered confusion with the large lymphocyte out of the question, but when the nucleus was not typically indented and was overlain with a few neutrophilic granulations, as occasionally appeared, confusion with the myelocytes might be conceivable, particularly in faintly stained specimens. On the other hand, with Ehrlich's stain the faintly staining nucleus which characterized the transitional, and the scarcity and type of granulation which was never seen to overlap the nucleus, distinguished this cell from the myelocyte but rendered confusion with the large lymphocyte possible on casual observation, in those cells with a nucleus not typically indented.

#### THE REACTION

This patient with syphilitic aortitis, having no untoward symptoms after the administration of one dose of salvarsan and a severe reaction manifested by a dermatitis, hepatitis, nephritis and probably phlebitis after a second dose five days later, presented a case unique in the fact that there was also a great increase in the typical transitional cells of the blood. No similar case has been encountered in the literature following any kind of arsenic therapy. Naegeli<sup>5</sup> mentions a number of conditions in which a transitional cell increase has been described, the greatest noted being 17 per cent in a case of lymph gland tuberculosis. Warfield<sup>9</sup> cites a fatal case of typhoid fever in which he counted 46 per cent of these cells, but this is most unusual, and the constant increase noted by Bunting<sup>10</sup> in early Hodgkin's disease has never been more than 17.8 per cent in his reported cases. The patient during the course of the illness also showed a pericarditis with

a typical friction rub and later with fluid, and a bilateral pleurisy with effusion, the former accompanied by an active leukocytosis

It will be observed (Fig 2) that the sharp rise of transitional cells was associated with a striking drop in the polymorphonuclears, but that the polymorphonuclear leukocytosis following later at the time of the pericarditis influenced the transitional curve only slightly. The characteristic precipitate descent of the polymorphonuclear curve after the subsidence of the acute process giving rise to the elevation, although synchronous with the falling curve of the transitionals, seems to be entirely without influence on it, the latter continuing the gradual descent noted both during the active polymorphonuclear leukocytosis and after the polymorphonuclear percentage had become approximately normal. Also, during the polymorphonuclear reaction, myelocytes were present in about the percentage to be expected, but at no time was a myeloblast observed, and at the end the blood was flooded with fragile forms incapable of being classified (see Table). These unclassified cells, by reference to the differential counts, seemed to be largely at the expense of the polymorphonuclears, and also to some extent of the transitionals and large mononuclears. However, proportionately allotted to these three groups of cells, they do not alter the curves materially (Fig 2). The lymphocytes, through both the reaction of the transitional and polymorphonuclear elements, showed only the variations normally to be expected, and these variations were entirely independent of the other reactions (see Table). The curve of the composite group classed as large mononuclears and containing many cells greatly resembling the transitionals, being above the curve of the transitionals, as is normal, both before the reaction and after it had subsided, was constantly below it during the reaction, and except for a slight rise at the time of the leukocytosis, maintained an almost constant level (Fig 2). At no time could enlargement of the spleen be made out by palpation or percussion and there was no variation in the slight general glandular enlargement noted on admission. No disturbance of the erythropoietic function occurred, as evidenced by the absence in the peripheral circulation of immature forms of red blood cells and the lack of polychromatophilia, etc.

#### DISCUSSION

The reaction of the blood in this case is interesting in reference to several views of the origin and status of the transitional cell. The initial fall of the polymorphonuclear curve coincident with the rise in the transitional seems at first sight to point to the transitional as one type of immature polymorphonuclear cell, but the subsequent sharp polymorphonuclear leukocytosis, associated as it was with the



presence of myelocytes and almost without influence on the transitionals makes such a view untenable. Also this cell seems to be independent of the myeloblasts and myelocytes, for it is improbable that such an intense transitional crisis could have been present without one myeloblast being noted if they are related forms, and the presence of myelocytes only in connection with the polymorphonuclear leukocytosis affords additional evidence in support of this observation.

The lack of any relation between the number of transitionals and lymphocytes throughout the entire transitional reaction speaks against any association with the lymphoid system.

The reaction of this cell was also independent of any change in the percentage of the large mononuclears, although it bore, as above noted, great resemblance to some of the cells included in the large mononuclear group. This one large mononuclear cell suggesting on morphological grounds an intimate relation with the transitional, presented all stages between its most remote form and the typical cell counted with the transitionals, and was entirely distinct from all other cells of the blood. Yet even this cell, though possibly present in slightly increased numbers, did not vary enough to influence the almost constant level maintained by the total large mononuclear count. However, we feel in agreement with Ehrlich<sup>15</sup> and many others that there is a close relationship between these two cells, and incline to the belief of Naegeli<sup>16</sup> that they should be considered together as one cell group. The common opinion that of these two cells the one with the indented nucleus, the true transitional, is the older form and develops from the cell of the more regular nucleus, is directly opposed to the evidence available in this case. For, in normal blood, in which one might expect the older forms in greater numbers, the mononuclear percentage is greater than the transitional. When the system was specially stimulated, bringing out, as one is justified in supposing, the younger forms, the increase was almost exclusively in the true transitionals.

In regard to the origin of the cell, it is of interest that no enlargement of the spleen or superficial lymph glands could be made out. The rich content of oxydase granules in the transitional cells is strongly in favor of the bone marrow as the point of origin. The scope of this paper does not permit a discussion concerning the confidence to be placed in the demonstration of oxydase granules as a diagnostic point between cells of the lymphoid and myeloid systems, but most studies seem to indicate that the differentiation is definite.<sup>15</sup> In this case no oxydase granules could be demonstrated in the lymphocytes, but they

<sup>15</sup> Gierke, E. Die oxydierenden Zellfermente, Munchen med. Wchnschr., 1911 lvm, 2315.

were present in great abundance in all transitionals and polymorphonuclears. It has already been mentioned that in the "indophenolblau" preparations for the demonstration of oxydase granules the distinction between the polymorphonuclears and transitionals was difficult in some instances. This uncertainty did not exist in regard to all the cells, however, and when a blood specimen showing 72 per cent polymorphonuclears and 54.4 per cent transitionals (together 61.6 per cent) as occurred in this case on March 4, contains oxydase granules in from 55 to 75 per cent of the white cells in smears made the same day, the observation that all transitionals contain oxydase granules seems reliably controlled. The possible presence of phlebitis makes one strongly consider an endothelial origin for these cells, for a process intense enough later to cause a phlebitis might readily be conceived as capable of first producing proliferative changes in the intimal endothelium. This origin seems unlikely, however, for although oxydase granules have been observed in many cells of the body, including the endothelial when fresh tissue was used, Gierke<sup>15</sup> was unable to obtain them in any but the cells of the tear and thyroid glands, and in those of myeloid origin after formaldehyd fixation and alkaline solutions, as used in this case. In the endothelial and other body cells it has been quite definitely proved to be a peroxydase, distinct from an oxydase reaction and depending on the labile respiratory oxygenase destroyed or inactivated by the above technic, whereas the stabile oxydase of the myeloid cells, being more resistant, endures<sup>16</sup>

#### SUMMARY

To summarize, the following observations were made on the reaction of the blood in this case

- 1 That the productive center of the so-called transitional cell was capable of *specific* stimulation

- 2 That there was a decrease in the polymorphonuclear coincident with an increase in the transitional cells but that this transitional reaction was not then or later accompanied by any immature cells of the polymorphonuclear system, and subsequent sharp polymorphonuclear leukocytosis, associated with a few myelocytes, was almost without influence on the number of transitionals

- 3 That the transitional cells, in contrast to those of lymphoid and endothelial origin and in common with those of known myeloid origin, contained oxydase granules in great abundance after formaldehyd fixation and with alkaline solution of the reagents

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16 For discussion and references see Gierke, Note 15

4 That there were no transition stages between any lymphocyte, large or small, and the transitional cell, and the specific stimulation of the transitionals did not influence the number of true lymphocytes in the blood

5 That although one type of large mononuclear cell bears a striking morphological resemblance to the transitional, only the latter was increased under the stimulation which occurred, and the total number of those cells going to make up the large mononuclear group was uninfluenced by the transitional reaction

#### CONCLUSIONS

While realizing that no definite statements can be made from the data afforded by a single case, in view of the unique opportunity offered by our case for study of the transitional cell we feel that the observations made strongly suggest the following conclusions

1 That the so-called transitional cell is not an immature or degenerated form of any other cell type, but is an independent cell type in itself

2 That the productive center of the transitional cell is closely related to that of the polymorphonuclear system, but is independent of it

3 That the transitional is not an endothelial cell, bears no relation to the lymphocytes large or small, and is probably of myeloid origin

4 That the one distinct type of large mononuclear closely resembling the transitional should probably be included with it to form an independent cell type, but that if there is any difference in the age of the cells of oval or indented nuclei, as seems likely, the cell with the indented nucleus—the typical transitional—should be considered the younger

I take this opportunity to thank Dr. Walter A. Baetjer and Dr. Thomas P. Sprunt of the staff of the Clinical Laboratory for their kindly interest and many helpful suggestions in the study of this case

ADAMS-STOKES SYNDROME — PERSISTENT BRADY-  
CARDIA INVOLVING BOTH AURICLES AND VEN-  
TRICLES REMARKABLE PROLONGATION OF  
THE As-Vs INTERVAL \*

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BALTIMORE

The patient, Mrs X, aged about 55, came under my observation on the 27th of April, 1913, in consultation with my friend Dr Hardin of Washington

At thirteen the patient had had scarlet fever, and six months later diphtheria, followed by more or less extensive paralysis. In other respects she had been a healthy woman and had had several children. For ten or twelve years, however, there had been some shortness of breath on exertion, and for eight months, frequent bleeding from the nose. For two months she had had peculiar periods of dizziness in which it had been noticed that her pulse was slow and irregular. Two weeks before she had had a sudden attack characterized by loss of consciousness and repeated slight convulsive seizures. Immediately after the attack the pulse was very slow, about 18 to the minute, and fairly regular. On the morning preceding the attack it had been 44, since the attack it had ranged between 28 and 35.

Examination showed a fairly healthy looking woman, lying on her back in bed. The pulse was regular, 36 to the minute. On inspection of the neck, by a rather poor light, there was a well-marked impulse in the jugular with each beat of the pulse, together with a second impulse, occurring at a point about midway between each beat. A satisfactory analysis of the jugular undulation was impossible because of the dimness of the light.

The heart was slightly enlarged, the sounds were clear throughout. There was heard, however, between each regular beat, a slight but yet distinctly audible sound. This occurred constantly about midway between the regular heart sounds, and had the general character of the sound which one commonly hears in association with the auricular contraction in heart block.

We were inclined to regard the condition as one of heart block with a 2:1 rhythm. Tracings were taken which are reproduced in Plates I and II. These tracings show, as may be seen, a bradycardia with an average ventricular rate of 33.7 to the minute. There is but

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\* Submitted for publication Sept 8, 1915

one auricular wave to each ventricular beat. That is, there is a like slowing of both chambers with *a-c* periods of unusual length. In twenty-three consecutive beats the *a-c* period ranges from 0.65 to 0.82 second in length, averaging 0.73 second.

The first, and most natural thought that came to one's mind was that this must, after all, be a 2:1 rhythm, and that, on careful examination, an elevation corresponding to a second auricular beat might be discovered somewhere on the tracing. And, indeed, rough measurements suggested, at first, that the sometimes prominent notch on the katacrotic limb of the *c* wave might possibly represent the beginning of a second *a* wave. For the differences in the periods separating the obvious *a* waves from the katacrotic notches on the succeeding *c* waves, and those between the latter and the next prominent *a* waves, were so slight that on first study of the tracings, we were inclined to accept this explanation.

A more careful study, however, shows that the consecutive *a* waves and the katacrotic notches on the *c* waves are not equidistant one from another, the distance from a given *a* wave to the succeeding notch being almost always slightly greater than that from the notch to the following *a* wave. Moreover, the *a* wave is a large, clearly defined elevation and the wave following the notch but slight and sometimes ill-defined. One is therefore obliged to assume that the condition is one of bradycardia involving both auricles and ventricles, and further, the remarkably constant relation between the *a* and *c* waves suggests that the chambers respond to a like impulse conveyed along the usual paths, with a remarkable delay in transmission. The impulses visible in the neck, and the sounds audible between the ventricular contraction were clearly associated with auricular systole.

Five weeks later, on the third of June, the patient came to Baltimore for further polygraphic and electrocardiographic study. At this time she appeared to be in excellent condition. The pulse was 36 to the minute, the blood pressure was high, by estimate about 180. In the jugular the same slight impulse was visible between arterial beats and with the arterial beat no definite presystolic impulse could be seen. The radials were not palpable. The point of maximum cardiac impulse was palpable in the fifth space, about 10 cm. from the median line, the dulness extending about 3 cm. to the right of the sternum. There was no retro-sternal dulness. At the apex there was a slight systolic murmur following the first sound, and between beats a soft, short sound was heard. This was loudest at about the juncture of the sixth rib and the sternum on the left, but was audible all over the cardiac area. The liver was palpable on deep inspiration, descending just below the costal margin.

Electrocardiographic records were first taken, after which the patient who seemed a little tired and short of breath, walked slowly up two flights of stairs where further polygraphic tracings were made. The electrocardiograms are reproduced in Plates III, IV and V. They show a bradycardia involving both auricle and ventricle, similar to that recorded in the polygraphic tracing five weeks before.

In Lead I (Plate III) the rate of the pulse is 35.9 to the minute, and the average P-R interval reaches the remarkable figure of 0.68 + second. The beats follow one another at regular intervals, and beyond the long P-R periods there is little striking about the record. The P waves follow one another at regular periods and there is no sign at any point of another P complex interfering with R or T elevations.

In Lead II (Plate IV), however, there are several variations from the usual relation and character of the P and R complexes. In this film the rate of the heart's action is 35.4 to the minute, and the average P-R time, 0.70 + second.

The R wave is inverted and has a rather flat summit with a notch in the middle. The P wave is large and triangular in form. The auricular beats are separated by a period usually varying from 1.6 to 1.7 seconds. At one point (*w*) after the ninth R wave on the record and 1.3 + seconds after the preceding P wave, there appears a small inverted deflection which has the general complex of a P. This is followed in 0.88 + second at *x*, by an erect P, somewhat smaller than the regular auricular complex, and this in turn is succeeded after 0.23 second at *y*, by an R deflection which differs distinctly in form from the ordinary R in the tracing. The next P follows at *z* after a shorter period than usual—1.08 + seconds—but occurs but little in advance of the time at which it would ordinarily have been due, and has its usual complex. Following this slightly precocious P elevation there is an unusually long P-R interval—0.88 + second—and the next P complex follows after a delay of nearly 0.2 second beyond the ordinary P-P interval. The P complexes, excepting the two at the points *w* and *x*, are quite similar in form. The R complexes occur at practically regular intervals throughout and at but one point (*y*) do they show any variation from their usual appearance.

In Lead III (Plate V) in which, unfortunately, but a short film was made, the heart's rate was 35.5 per minute and the P-R interval averages 0.69. There is nothing striking about the appearance of this film. The R and T waves are inverted. The P waves are smaller than in Lead II, of much the same general appearance as in Lead I.

The next record was taken with the Mackenzie polygraph (Plate VI). The patient seemed a little nervous and tired and had walked up two flights of stairs. The pulse rate had become slower—31.3 to

the minute. The average *a-c* interval was  $0.79 \pm$  second. The general appearance of the tracing was exactly similar to that taken on April 23, but at two points slight irregularities were noted, associated, I think, with swallowing or some other movement. At the first of these points (*x*) regular *a* and *c* elevations can be made out, although the former is immediately preceded by an unaccountable wave. The succeeding *a* is separated from the next *c* by an unusually long period. At the second point (*y*) there is an elevation preceding the *v* wave, and the latter is followed by that which appears to be an *a* occurring at a remarkably precocious period, and separated from the succeeding *c* by a very long space of time. Although no special notes were made on the tracings at the time when they were taken, the irregularities at *x* were, I think, dependent on movements of some sort, for I remember distinctly that although the tracings were rather carefully studied, no serious irregularity was noticed at the time. It may be that the elevation at *z* represents a precocious auricular systole similar to those on Lead II of the electrocardiogram, but I am disposed to regard it as an artefact. Nothing similar was observed on the rest of a fairly long tracing.

Lastly, carotid and jugular tracings were taken with a Verdin polygraph (Plate VII). There was some difficulty in obtaining a satisfactory record. The patient became rather nervous and tired. The rate of the pulse is here 28.8 to the minute, while the *a-c* interval varies from 0.81 to 0.97 second, reaching the remarkable average length of 0.886. Excepting for the slower rate of the pulse, and the remarkably long As-Vs interval, the tracing differs in no essential from those made with the Mackenzie instrument.

How are we to explain these remarkable records? Are we to assume that we are dealing with an instance of complete heart block with idio-ventricular rhythm, or are we to fancy that the stimulus for each contraction has developed at the normal point and that we have before us an example of simultaneous slowing of all chambers of the heart with an auriculo-ventricular conduction time amounting in some instances nearly, if not actually, to one second, and with a P-R interval which averages between 0.6 and 0.8 second?

In favor of the former assumption we might regard the rate of the heart, 29 to 35 to the minute, almost exactly that of ordinary idio-ventricular rhythm, as well as the circumstance that in Lead II of the electrocardiogram where, at one point, two atypical auricular complexes occur, the ventricular rhythm remains essentially unaltered. But strongly against such an explanation seems to me the circumstance that in a series of tracings taken after an interval of five weeks, the relations of auricular and ventricular contractions remain almost the same. It is hardly conceivable that at such varying periods of time,

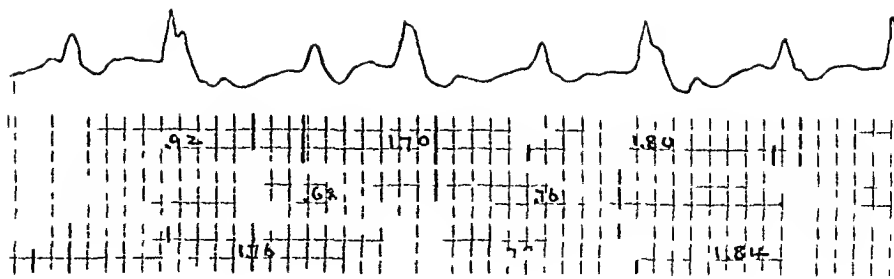
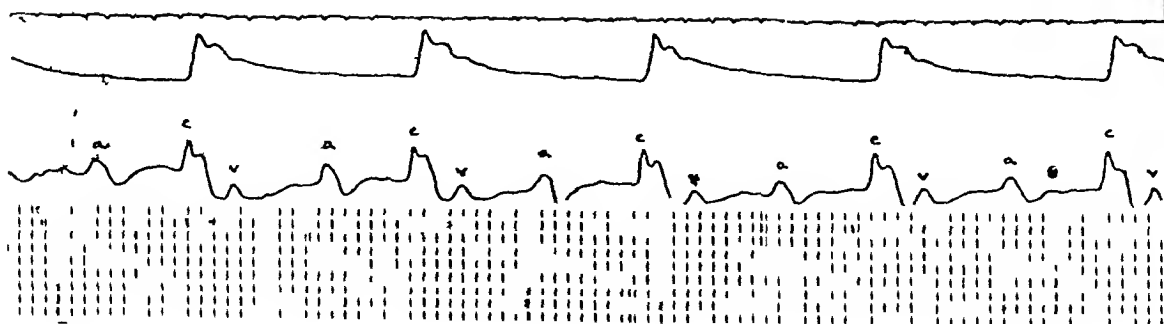
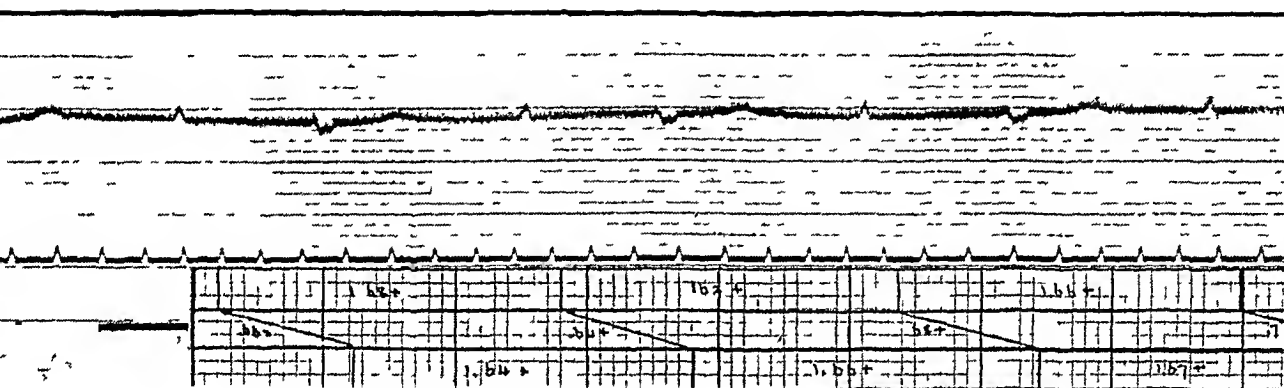
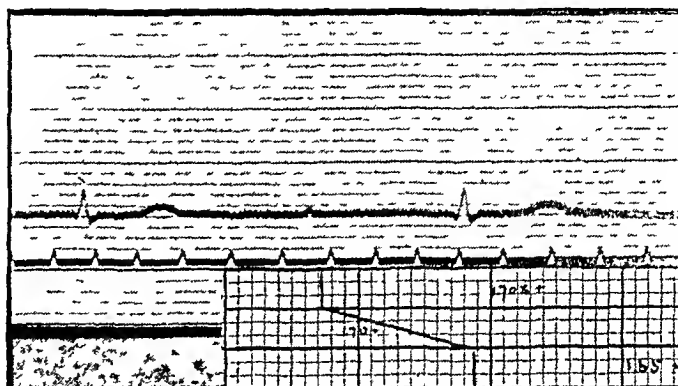
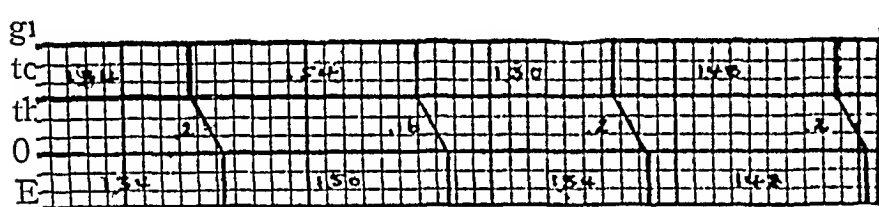
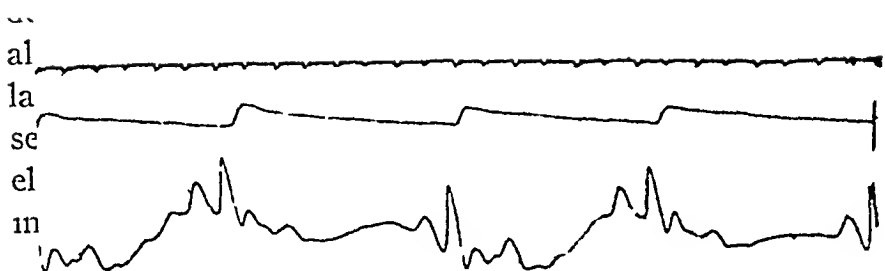


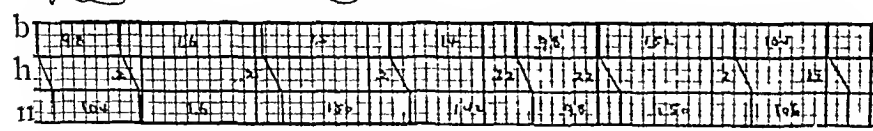
Plate I



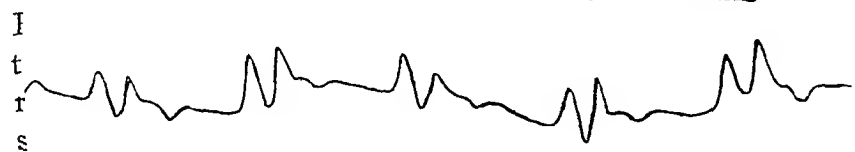
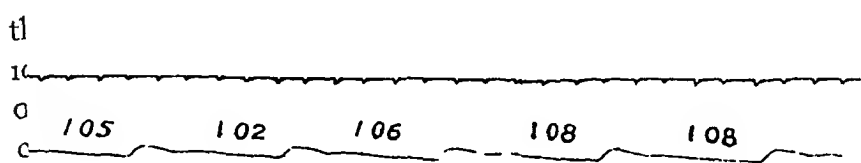




A  
tl time, 19 + sec



w time, 20 +



.o) Rate, 57 6

and in so many tracings, the relation in time between the *a* and *c* waves and the P and R complexes should have been so constant unless auricular and ventricular action were controlled by common stimuli

Another argument in favor of this assumption would seem to be the character of the R wave in the electrocardiogram. This does not present the diphasic excursions commonly seen with idio-ventricular rhythm, but has rather more the appearance of a complex dependent on a stimulus carried from above along the bundle

How may one explain the events on Lead II of the electrocardiogram?

The first inverted P complex (*w*) is probably an auricular extra-systole

How are we to explain the abnormal complexes associated with the following P and R elevations? It would not seem probable that a P-R interval so short as 0.23 second could represent a true conduction time when, throughout the rest of the film, the P-R interval is never shorter than 0.64 second, unless it be that we fancy that the P elevation here is an extra systole arising in the node or bundle. In extra systoles arising in junctional tissues, the P and R elevations are usually, it is true, much more closely associated. But might not the delay in this instance reasonably be explained by the anomalous conditions which are accountable for the remarkable length of the P-R interval during the regular cardiac action? The suggestion that the P wave at *x* is an extra systole is supported by the slight variation in its complex, which has already been mentioned

Following this extra systole, the next regular stimulus represented by the P elevation at *z*, occurring after a shorter period than usual and meeting with an exhausted bundle, is followed by an unusually long P-R interval—0.88 second

The variation in the R complex at *y* suggests, however, another possible explanation. Might it not be that this complex represents an idio-ventricular contraction quite unassociated with the impulse responsible for the preceding P? The sequence of events then might be as follows. A precocious auricular systole at *w* in a heart in which, owing to disease of the bundle, the P-R time is greatly delayed finds the bundle refractory and is blocked. At *x* there occurs a second auricular contraction at a period fully 0.4 second later than that at which the regular auricular contraction should have occurred. Owing, however, to the long continued bradycardia at a rate close to that of ordinary idio-ventricular rhythm, the heart is continually on the threshold, as it were, of idio-ventricular impulse formation. And indeed, after a delay slightly longer than usual, such an idio-ventricular contraction

occurs at y, at a period considerably in advance of the time when the stimulus responsible for the auricular contraction at a might have been expected to produce a ventricular response

An exceptionally interesting feature of these tracings is the great prolongation of the As-Vs interval in the last tracing, in which the average *a-c* period was 0.886. On the whole we see a gradual slowing of the pulse from beginning to end of the records taken June 3, a diminution in the rate from 35.9 to the minute at the beginning of the electrocardiographic records to 28.8 to the minute in the one successful tracing which was obtained with the Verdin instrument, this course of events suggests the possibility that physical exhaustion may have resulted in slowing of the cardiac rhythm and delay in the conduction time

I have, unfortunately, been unable to see the patient since June, 1913. In July of that year she had two attacks of vertigo with unconsciousness and convulsions lasting several minutes. At the time of the attack the pulse was slow and irregular, immediately afterwards it varied from 28 to 50. Dr. Hardin writes me

"In June, 1914, she had three more severe convulsions, one at three o'clock in the morning, another six hours later and another early the following morning. Following these convulsions there was continuous and violent vertigo markedly increased by raising her head from the pillow, and lasting for eight days.

"The next and last attack was on the 17th of February, 1915, when she fell in her bathroom and was unconscious for some time following. I have never seen her in one of these convulsions and have been unable to secure any definite data from any of those who have witnessed the attacks. Her pulse has varied from 28 to 44 when we have seen her during the past winter and she complains almost continually of mild vertigo and a sense of confusion and uncertainty in her head."

We have waited nearly two years before presenting these records in the hope that it might be possible to continue our observations. Unfortunately, the patient's family have consistently refused to allow further polygraphic or electrocardiographic studies.

It was early felt that it might be well to try the effect of large doses of atropine but unfortunately the patient shows an unusual idiosyncrasy towards the drug. Dr. Hardin writes

"The minutest dose poisons at once. I have tried it several times when she is unsuspecting. I have seen  $\frac{1}{600}$  of a grain (0.00013) of atropine and also one drop of the tincture of belladonna flush her face and dilate the pupils so that she cannot see at all, produce great restlessness, insomnia and excitement for hours and hours."

Clinically the course of events was typically that of an Adams-Stokes syndrome, and it would seem from the history as if at the time of the syncopal and convulsive attacks, there may well have been long

intermissions in the pulse On the two occasions in which we have been able to study the patient, however, there has been no actual auriculo-ventricular dissociation, but a slowing of both auricles and ventricles to a rate of from 28 to 35, about that of the ordinary idio-ventricular rhythm, with a great prolongation of the As-Vs interval The remarkable As-Vs interval, as well as the rate of the pulse might lead one to suspect a true dissociation, and the circumstance that in Lead II of the electrocardiogram, despite irregular auricular contractions at one point, the ventricle continues its regular rate, might support such an hypothesis

On the other hand, the constancy of the As and Vs relations, which remained unchanged for an interval of five weeks, would be almost inexplicable unless we assume that the contractions of both chambers are governed by a common impulse Again, the R complexes are of such a character as to lead one to believe that they are dependent on a supraventricular stimulus The one serious objection to this assumption, that based on the regularity of the ventricular rate at the time of the auricular extrasystoles in Lead II of the electrocardiogram, would not seem to be serious if we regard the ventricular complex at *g* as a single idioventricular contraction arising after a very slight delay, in a heart muscle the rate of contraction of which has been for a long time so slow that it has been continually on the threshold of idioventricular stimulus formation—an hypothesis which is supported by the character of the complex

The unprecedented length of the As-Vs interval—*a-c* periods averaging over 0.7 second and reaching at some points nearly, if not quite, one second in duration—P-R intervals often exceeding 0.7 second, can hardly be used as an argument against our interpretation of the manifestations For although we are unaware that As-Vs periods so long as this have been previously observed, yet Griffith and Cohn,<sup>1</sup> and Peabody and the writer<sup>2</sup> have recorded instances in which the *a-c* interval has amounted to from 0.5 to 0.6 second

What may be the pathological basis for such remarkable functional manifestations? From the data at hand, it is obvious that one can but speculate The great lengthening of the As-Vs interval and the history of the syncopal and eclamptic manifestations would suggest disease of the *a-v* bundle But how shall we explain the slow auricular rate? Despite the general regularity of the auricular beats and the

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1 Griffith, T. W., and Cohn, A. E. Remarks on the Study of a Case Showing a Greatly Lengthened *a-c* Interval with Attacks of Partial and Complete Heart-Block, with an Investigation of the Underlying Pathological Conditions, *Quart Jour of Med*, 1910, *iii*, 126-151

2 Thayer, W. S., and Peabody, F. W. A Study of Two Cases of Adams-Stokes Syndrome with Heart-Block, *THE ARCHIVES INT MED*, 1911, *vii*, 289-347

persistence of the phenomenon, abnormal vagus influences cannot wholly be ruled out. One might fancy that there were changes which had resulted in a 2:1 sino-auricular block, but with the information at hand this can only be advanced as an hypothesis without supporting evidence.

Instances of permanent slowing of the auricular action to a rate below 40 with regularity, are by no means common. Such an instance I had the opportunity to study several years ago.

S., aged 30, a civil engineer, consulted me on the 21st of October, 1910, complaining of nausea, dizziness and "sinking spells." He had been a rather heavy smoker, consuming as many, sometimes, as fifteen cigars a day. He had worked very hard at his profession. He had been married four years and had two children.

He had had no serious illnesses in childhood and had never been subject to tonsillitis. As a child he had not been allowed to exercise very vigorously because, as he said, he had not "grown up to his heart." At college he took up rowing, but was generally taken out of the boat for some reason or other before the competitions. He had never suffered from palpitation, dyspnea or coughing.

For five years his physician had noticed that his pulse was slow, ranging usually between 44 and 52. Early in May, five months before I saw him, while under an unusual stress of work, he had an attack of vertigo on the golf links which obliged him to lie down on the ground. After about two minutes he was able to arise and finish the game. A week or two later there was a similar attack while sitting in a chair at dinner, so that he fell forward onto the table. This was followed by several like attacks at intervals of about ten days, and in the first week in July he had a very severe paroxysm in the street car. The attack lasted while the car was passing about three blocks, he did not fall from his seat. After these attacks he was very weak and felt that he must lie down.

At the time of the attack in the street car he was seen by an excellent physician who found a ventricular rate of 32 to the minute, and what appeared to be a double venous impulse in the neck, suggesting a heart block with a 2:1 rhythm. He then went to the mountains, spending some days quite at rest. At this time his family physician found his pulse from 32 to 36. In twenty-four hours the pulse had risen to 42. A few days later, on the 15th of July, he had a nervous attack associated with a sense of sinking, feeling very weak, as he expressed it, "as if my blood were all going out." His physician states that his pulse was again 32.

Although there was no history or evidence of lues, he was treated with mercury and iodide of potassium with apparent improvement until August 1, when he had another "sinking spell" which was repeated again two weeks later. At these times the pulse ranged from 28 to 32. The patient suffered also from a feeling of nausea in the morning and felt rather dizzy, but was inclined himself to feel that his dizziness was nervous. From the 15th of August he gradually improved and now, October 21, feels perfectly well.

In my consulting room the patient appeared a healthy man. Nothing abnormal beyond the cardiac conditions was found. The pulse was between 30 and 35, essentially regular. Now and then a beat occurred at a period a little earlier than it might have been expected, but was followed by no compensatory pause. Inspection of the neck showed a normal venous undulation, all three waves being plainly visible. The patient was a well nourished man over 6 feet tall. The heart was a little large, the impulse easily palpable in the fifth space, 11.5 cm. from the median line, slightly within

the mammillary line, relative cardiac dulness, 33 cm to the right of the mid-sternum. The first sound was prolonged and followed by a slight, indefinite systolic murmur, heard in the axilla and rather louder over the base, the second sounds were clear and of normal relative intensity. The murmur was less intense in the erect posture, and barely audible at the apex, not heard in the back. The heart was normally mobile, occasionally, as the patient was lying on the left side, a third sound could be heard.

Polygraphic tracings with the Mackenzie instrument showed marked bradycardia involving both chambers of the heart, no extra auricular beats were to be seen, the *a-c* time was normal. The patient entered the hospital for study. A radiographic examination of the chest revealed nothing abnormal.

The urine and blood showed no abnormalities. The Wassermann test gave a negative result. Radiographic examination of the chest showed nothing unusual.

While lying quietly in bed the pulse varied in rate from 28 to 35. The rhythm, though essentially regular, showed, at times, variations consisting of occasional precocious beats suggesting sometimes extrasystoles. These beats were not, however, followed by compensatory pauses, (Plate XII) and, on the whole, were suggestive of an ordinary sinus arrhythmia.

Respiration was associated with the normal changes in rate, and exercise and emotion accelerated the pulse in the usual manner, but rarely, if ever, to a rate above 50 to the minute. The slight irregularities in rhythm were somewhat more evident after exercise. It is not impossible as suggested by my colleague, Dr. Bridgman, that this exaggerated irregularity is associated with respiration.

Numerous polygraphic tracings showed little beyond the bradycardia.

The tracing reproduced in Plate VIII, taken when the patient was at rest, shows an essentially regular pulse at the rate of 31.7, with a normal *a-c-v* sequence. The *a-c* interval is a shade long,  $0.21 \pm$  second. In the next tracing taken a little later, after exercise (Plate IX), the rate of the heart is 43.2. The *a-c* interval averages  $0.19 \pm$  second. There is an interesting alternation in the length of the intersystolic periods. This phenomenon was, however, not observed at any other time in our study of the patient. In the following tracing (Plate X), taken after a short pause to adjust the receiving cup over the jugular, the pulse has already fallen to 31.8 and this alternation is no longer evident, while in later records (Plate XI), taken after exercise, no such alternation is seen, although the rhythm shows considerable irregularity.

Atropine 0.0011 (gr  $\frac{1}{60}$ ) and 0.0016 (gr  $\frac{1}{40}$ ) administered subcutaneously produced little or no effect on the heart's action. After 0.0022 (gr  $\frac{1}{30}$ ) the pulse rate increased gradually to 60. A polygraphic tracing continued for over half an hour after the injection, showed no abnormalities (Plates XII and XIII). It was, unfortunately, impossible to obtain electrocardiographic records as the instrument was out of order.

Since this period the patient has seemed physically well, but the pulse has always remained at a rate between 30 and 40 while at rest. I last saw the patient about two years ago as he was about to go on the table for an appendectomy. The pulse at this time was 32, and the venous undulation in his neck, perfectly normal. He passed through the operation without ill effect. His physician, Dr. E. P. Carter of Cleveland, who has studied the patient carefully, and confirmed these observations, writes (July, 1915)

"S is very well, active and busy. His pulse when last taken by me in May, was 39 to the minute. Polygraphic records have never shown any increase in his *a-c* interval. he has had no attacks of dizziness since you saw him."

Here then we have the history of an individual the rate of whose cardiac action has apparently diminished gradually through a period of years, until, five years ago, it reached a permanent rate of but little over 30 when at rest, a rate which has been maintained since that time.

At one period, five years ago, after excesses in work and tobacco, there were several attacks of vertigo and nausea. The pulse, at these times, was a little over 30 and regular. With improvement under rest there was, however, no change in the rate of the heart's action, and the pulse remains today, when the patient appears to be in perfect health, at essentially the same rate. In polygraphic tracings the *a-c* interval is normal and beyond slight sinus irregularities in rhythm which are increased on exercise, nothing of note is revealed.

What are we to regard as the cause of the bradycardia?

It is hardly possible to ascribe it to vagus influences, for experiment shows that the vagus influences are essentially normal. Respiration is followed by the usual variations in rhythm and atropine produces its usual effect, *proportionately, however, to the initial cardiac rate*.

One is hardly justified, in the present state of our knowledge, in assuming the possibility of a persistent sino-auricular block—an hypothesis against which one might advance further the essential regularity of the pulse through such long periods of time, as well as the gradual increase in rate, without irregularity following atropine. One would fancy that we are here concerned with an essentially slow stimulus formation, with a so-called sinus bradycardia, a bradycardia depending on chronotropic influences solely.

But in what do such influences consist? Is the condition to be regarded as pathological or only as anomalous?

These are questions which must be answered by time and by further study.

To what were the phenomena of vertigo and nausea due? The physicians who observed the patient at the time of these attacks were at first under the impression that a wave possibly indicating an auricular contraction, was to be seen in the jugular between each regular beat. If this observation of his physicians was correctly interpreted we must assume that, at this time, there was a true heart block—a 2:1 rhythm. The absence of prolongation of the *a-c* interval is no proof that such a condition may not have existed. One would, however, hardly expect vertigo with a regular pulse of thirty and above, unless this slow pulse followed suddenly on a rate considerably more rapid—unless, say, it were a question of a sudden halving of the pulse rate. May this have occurred at the time of these attacks?

Such an hypothesis might be advanced to explain the phenomena observed in this patient. I have seen a similar sequence of events in an individual with chronic myocardial disease, whose pulse when at rest, was in the sixties. Any effort, such, for instance, as sitting up and down several times in bed, was followed by a slight increase in the auricular rate with the dropping out of every other ventricular

contraction After a few moments' rest the regular As-Vs sequence was resumed At no time was there any prolongation of the *a-c* interval

Experimentally, however, in the present case, it was impossible to reproduce any such phenomenon by exercise or atropine, and even with vigorous exercise the pulse rate was never observed at a point above sixty It is a question whether the apparent double auricular impulse in the jugular may not, perhaps, have been simulated by the large and very evident *v* wave, indeed such now is the opinion of the physician who has had the patient constantly under observation

On the whole the writer is inclined to agree with him and to doubt whether any actual auriculo-ventricular dissociation has ever occurred in this patient He is disposed to regard the vertigo and nausea as the results of a generally overwrought mental and physical state in an individual who might well be predisposed to such symptoms because of his anomalously slow heart action

To what this remarkable bradycardia may be ascribed is a question which, as has been said, cannot definitely be answered

The phenomena observed in this patient are similar to those described in Mrs X mainly in that in both there is a striking bradycardia involving both chambers of the heart

In the former patient (Mrs X) both the history and the results of physical examination revealed evidences of grave disease of the *a-v* bundle—Adams-Stokes syndrome with extreme slowing and irregularity of the pulse and remarkable prolongation of the As-Vs period In the second patient, however, there was no lengthening of the As-Vs interval and, despite the history of vertigo and nausea, there was no evidence that auriculo-ventricular dissociation had ever occurred Indeed, the symptoms pointed, rather, to an unexplained sinus bradycardia

#### SUMMARY

The history is presented of a woman who for two years and a half has had occasional syncopal and eclamptic attacks with extreme bradycardia

Between these periods the pulse is regular, averaging (in rate) but little over 30 to the minute

Polygraphic and electrocardiographic study reveals a synchronous slowing of both auricles and ventricles with prolongation of the As-Vs interval to a period longer than has hitherto been reported In polygraphic tracings the *a-c* interval amounts to from 0.7 to 1.0 second, in electrocardiograms the P-R time is often over 0.7 second

The history of syncopal and eclamptic attacks with great slowing and irregularity of the pulse, as well as the prolonged As-Vs interval



observed in our studies, justify a diagnosis of disease of the auriculo-ventricular bundle. The cause of the auricular bradycardia which would appear to depend on an essential anomaly of impulse formation, is not clear.

A second case of apparently essential sinus bradycardia is reported.

This subject is a seemingly healthy man now 35 years of age. The heart rate for at least five years, has been between 30 and 40 when the patient is at rest. There is no prolongation of the As-Vs interval. Exercise, deep breathing, atropine have their usual effects on the heart's rhythm and rate, but proportionately to the initial cardiac rate.

Attacks of vertigo and nausea occurred five years ago but there is no evidence that these were associated with auriculo-ventricular dissociation. The patient remains in apparently good health despite his persistent bradycardia.

I am indebted to my colleague, Dr. Bond, for the electrocardiograms in Case 1.

Plates I, II and VI were, owing to an unfortunate mistake, reinforced by hand over the original tracing before reproduction, a circumstance which accounts for certain irregularities in the line of the tracing.

# THE TYPHOIDIN QUOTIENT

## QUANTITATIVE STUDIES OF THE CUTANEOUS TEST OF TYPHOID IMMUNITY<sup>\*</sup>

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In view of the uncertainty about the duration of immunity conferred by antityphoid inoculation and the occasional occurrence of typhoid fever among those recently vaccinated, it is highly desirable to have a test which will indicate the existence or absence of immunity and if possible also the degree of immunity. Gay and Force<sup>1</sup> have discussed the heretofore unsatisfactory efforts to utilize agglutination and other biologic reactions for this purpose, and have described promising experiments with a cutaneous typhoidin test.

The technic used in this investigation was described by Gay and Force<sup>1</sup> and is similar to the Pirquet tuberculin test. It consists in making two circular abrasions without drawing blood by rotating a chisel with a 2.5 mm blade. "Typhoidin" was applied to one spot and the control application to the other. The preparation of killed typhoid bacilli in liquid culture medium having been found by Gay and Claypole<sup>2</sup> to deteriorate on standing, the same was dried and ground and a small particle of the powder rubbed into the abraded area with a sterile toothpick.<sup>3</sup> The control application consisted of a similar preparation of the culture medium (glycerin-bouillon) without the typhoid organisms. The reactions were examined after about twenty-four hours. In order to minimize the personal factor in interpreting these results and to obtain figures as objective as possible, the reactions were not recorded as "positive" or "negative," but only the diameters of the areolas were put down. Usually at least a small blush could be observed about both the control and the typhoidin spots, and the great-

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<sup>\*</sup> Submitted for publication July 21, 1915.

<sup>\*</sup> From the Departments of Medicine and of Pathology and Bacteriology, University of California.

1. Gay, F. P., and Force, J. N. A Skin Reaction Indicative of Immunity Against Typhoid Fever, *THE ARCHIVES INT. MED.*, 1914, xiii, 471.

2. Gay, F. P., and Claypole, Edith M. An Experimental Study of Methods of Prophylactic Immunization Against Typhoid Fever, *THE ARCHIVES INT. MED.*, 1914, xiv, 671.

3. It is still too early to state definitely the potency and keeping qualities of the dried typhoidin. Further experiments on this question are to be undertaken in the Department of Pathology and Bacteriology. The typhoidin here employed had been prepared one year previously.

est diameter of each was measured. For this purpose a machinist's vernier gage was used, which reads to 0.1 mm., and which enables the observer to set the instrument to the required measurement without seeing the result until afterwards. Papule formation was disregarded in the analysis, since it is not subject to the same objective interpretation and only occurs when there is a well-marked areola.

Because the areolas never have absolutely sharp edges, the subjective element in gaging the two spots is not removed by these measurements, though it is undoubtedly materially lessened. It is also quite evident, however, that as cutaneous diagnostic tests have been used, the greatest play of judgment has occurred, not in estimating the comparative size of the areolas, but in the subsequent decision as to whether or not the comparison warrants reporting the test as "negative," "positive," "weakly positive," etc. The actual measurement of the areolas makes it possible by reporting merely the relation between two quantities to eliminate entirely this latter uncertainty.

The most obvious ways of expressing mathematically this relationship are to combine either the two surface areas of the areolas or the two diameters to form either a difference or a quotient. Without going into the theory of local allergic phenomena, it may fairly be considered probable that the intensity of the biologic mechanisms responsible for dilatation of small blood vessels is related to the distance from the inoculated points to which hyperemia extends (radii or diameters of the areolas) rather than to the number of arterioles involved (surface areas). As to the mathematical relationship to be used for connecting the diameters—if the control reactions were always the same, it would be proper to suppose that the intensity of the biologic reaction to the typhoidin was more or less proportional to the excess of the test-areola diameter over that of the control spot, i. e., that the difference between the two diameters should be used as a basis for comparison. But the fact that there is considerable individual variation in the reactions due to the trauma of the chisel itself, with or without the control application, suggests that there is a corresponding variability in the extra extension of the hyperemia by the typhoidin, independent of any immunity mechanism. If this is true, it follows that the ratio of one diameter to the other is a better index of the relative intensity of the reaction. This ratio (diameter of the typhoidin spot divided by that of the control) may be termed the *typhoidin quotient*. Whatever its merits, it will be realized that the process of obtaining the typhoidin quotient is exactly what is attempted subconsciously whenever one interprets such reactions by simple inspection. For example, if in a given case the control diameter is 2 mm. and that of the test spot 4 mm. the reaction will invariably be judged

positive, whereas with the same or even greater difference in the diameters the test will be considered negative or doubtful if the areolas measure 10 or 12 mm. The parallelism will be noted to the well known Weber-Fechner psychological law governing sensations.

Considerable experimental evidence will of course be required before it can be stated that these quotients indicate relative degrees of protection against typhoid fever, though in a general way this may be expected to prove true. What is urged is that it is possible, not only

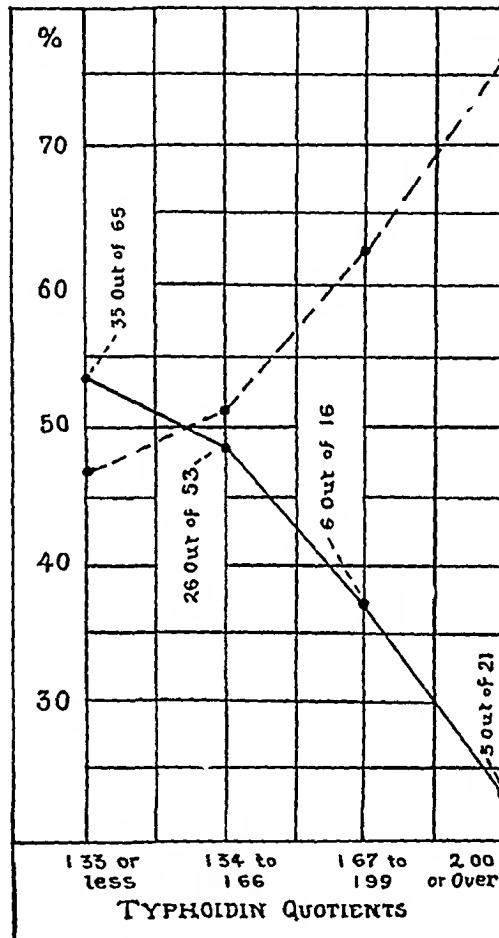


Fig 1—Relation of the typhoidin quotient to the previous history of typhoid fever or vaccination. Dotted line indicates those supposed to be immune, solid line the nonimmunes. Numbers at bottom show the four classes according to typhoidin quotients, figures at left show percentages in each group.

in typhoidin but also in tuberculin and other related cutaneous tests, to eliminate much of the observers' personal element by reducing to figures the process of "reading" the reactions. In view of this increased objectiveness and the way thus opened for quantitative analyses, it is felt that at least for purposes of record and reporting, these quotients deserve to come into general use. Clinical records of cutaneous reactions to be complete should give both of the diameters and their decimal quotient.

The diameter of the chisel has not been deducted from the diameters of the two areolas before computing the quotient, for the reason that this quantity in both dividend and divisor keeps the quotient within reasonable bounds (otherwise it would approach infinity when the control reaction was slight or absent) and in no way interferes with its usefulness. Chisels should of course be of uniform width.

The subjects consisted of 162 individuals, fifty-eight women and 104 men, who were mostly from among the staff, students, nurses and employees of the University of California Medical Department and Hospital, and from the departments of dentistry and pharmacy. Most of them were young adults, a few were middle aged.

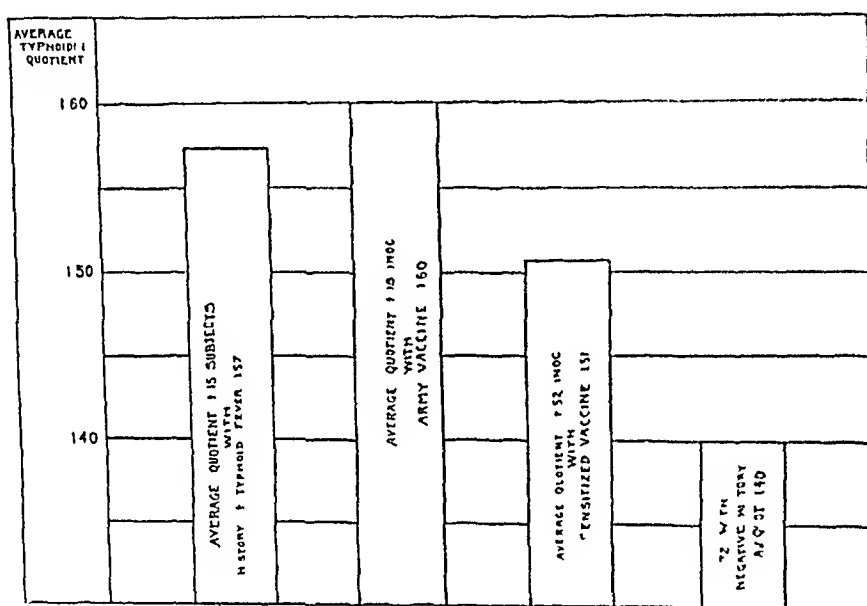


Fig 2—Average of typhoidin quotients of immunes, those who have had typhoid fever, those who have had army vaccine, and those who have had sensitized vaccine

#### RELATION OF THE TYPHOIDIN QUOTIENT TO THE HISTORY OF PREVIOUS TYPHOID FEVER OR VACCINATION

For showing this relation the cases were divided into four groups according to their typhoidin quotients. The first group consists of sixty-five persons with typhoidin quotients 1.33 or less, the second of fifty-three with quotients from 1.34 to 1.66, the third of sixteen with quotients from 1.66 to 1.99, and the fourth group of twenty-one with typhoidin quotients of 2 or over. The solid line of Figure 1 shows the percentage of supposedly nonimmunes in each of these groups. The numbers at the left indicate percentages, those at the bottom the groups according to typhoidin quotients. In connection with each dot indicating a percentage the number of cases in the group is given and the number of nonimmunes, that is, the figures from which the corresponding percentage is obtained. The dotted line shows the percent-

ages of those in the different groups who have been vaccinated against typhoid, or who have had typhoid fever. From the figure it will be seen for example, that for a subject with a typhoidin quotient of from one to one and two-thirds, the chances that he belongs to the immune or nonimmune group are about equal, while if his typhoidin areola is at least twice the diameter of the control (quotient 2 or over) the chances are about three out of four that he has had typhoid fever or vaccine.

The vaccinations were all from one-half to two and one-half years previous to the test, the cases of typhoid fever dated back from a few weeks to twenty-five years. Those who had had typhoid fever or different kinds of antityphoid vaccination were not numerous enough in the different groups to warrant separate comparisons.

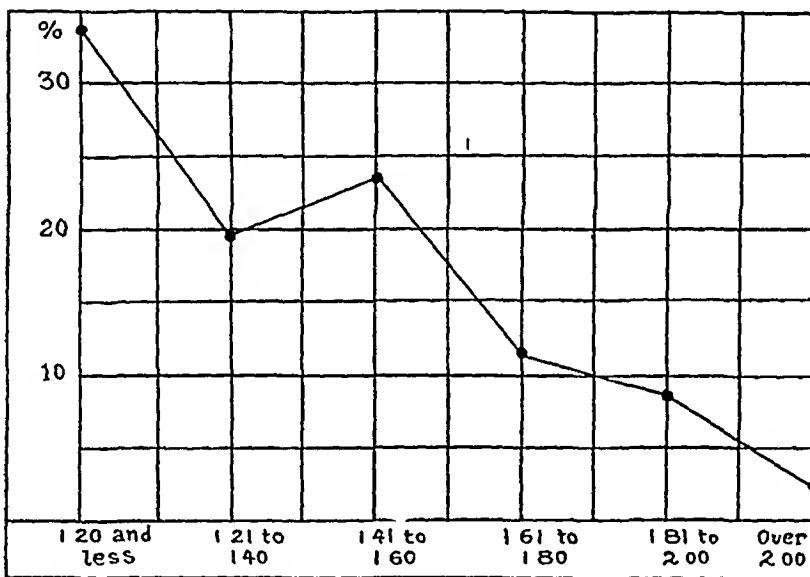


Fig. 3—Variation in typhoidin quotients among supposedly nonimmunes, that is persons with "negative" history. Numbers at bottom indicate groups separated according to typhoidin quotients, at left percentages of the total number of the nonimmunes (seventy-two).

Figure 2, however, shows the relation of typhoidin quotients from a slightly different point of view, the average quotients being charted separately of those with negative history (72 cases), those who had had typhoid fever (15 cases), those who had had army vaccine (18 cases), and those who had received the sensitized vaccine of Gay and Claypole<sup>2</sup> (52 cases).

Those with history of typhoid fever and those who have had army vaccine have nearly the same average quotients, about 1.60; those with negative history have the lowest average, 1.40, while those who had received sensitized vaccine have an intermediate average. The lower average quotient for the sensitized vaccine group is notwithstanding the fact that the majority of these subjects were vaccinated from one to two years ago, while most of those who had had army vaccine were vaccinated two and one-half years ago.

The seventy-two who denied having had antityphoid vaccination or typhoid fever (in questioning the subjects care was taken to rule out so far as possible unrecognized typhoid) had typhoidin quotients ranging from 0.75 to 2.50 and averaging 1.40. The distribution of these values is shown in Figure 3.

A certain percentage of individuals with negative history have had unrecognized typhoid fever. Sawyer<sup>4</sup> and Gay and Claypole<sup>5</sup> have shown that these cases may be considerably more numerous than has been commonly supposed, and they may account for a certain number of the high quotients in persons with negative history. Figure 3 shows, however, that in the vast majority of the negative cases the reaction is definitely more to the typhoidin than to the control application, so that the reaction can hardly be called even "probably positive" unless the quotient is well over 1.50. It may be added that Figure 3 showing the wide variation of values in the "negative history" group is fairly representative of conditions in the different groups of supposedly immunes.

A few of the low quotients in persons who give a history of having had typhoid fever may be accounted for by mistaken diagnosis, but probably most of them should be considered as failures of the test. One physician with quotient of 1.00 had typhoid fever with positive Widal three years previously. A hospital patient with a quotient of 1.11 had had proved typhoid fever, which subsided about seven weeks previously—possibly his typhoidin reaction would be stronger at a later date.

Gay and Force in some instances found typhoidin reactions appearing as early as six hours and early fading. This I believe to have been true in some of the cases in this series and possibly a few of the failures may be thus accounted for, but the six-hour observations which it was possible to make were so few that it was thought better to omit them entirely from the analysis.

From Figure 3 it will also be seen that it is not the occasional case that departs far from the general average, but that there is a very general wide scattering, so that the probable error in any given case is large. This has been determined to be 0.22 by the use of the following formula:<sup>5</sup>

$$\text{Probable error of a single observation} = \pm 0.6745 \sqrt{\frac{S}{n-1}}$$

when  $S$  = the sum of the squares of all the quotient differences from the mean, and  $n$  = the number in the series. That is, in any given

<sup>4</sup> Sawyer, Wilbur A. *Ninety-Three Persons Infected by a Typhoid Carrier at a Public Dinner*, Jour. Am. Med. Assn., 1914, LXIII, 1537.

<sup>5</sup> Stewart and Haldane. *Elementary Practical Physics*, Edit. 2, p. 267.

case in this group the chances are even that the quotient will differ from 1.40 (the general average) by more or by less than 0.22

The probable error in the average quotient itself is 0.045 as determined by the formula

$$\text{Probable error of the mean of the whole} = \pm 0.6745 \sqrt{\frac{s}{n(n-1)}}$$

That is, the chances are even that the true average quotient for nonimmunes, supposing it to be based on thousands of observations, would lie within or without the limits 1.355 and 1.445. As stated above, this amount of variation in the quotient values among nonimmunes is representative of the typhoidin quotient variability among the immunes.

#### CONCLUSIONS

1 The use of typhoidin, tuberculin and other "quotients" in interpreting cutaneous diagnostic reactions is urged, for the reason that objectiveness is thus increased and quantitative analyses made possible.

2 In individual cases the test as here used has a high probable error and is therefore not conclusive.

3 It has a neutral significance when after twenty-four hours the typhoidin quotient is in the region of 1.40 to 1.50, that is, when the typhoidin spot is about one and one-half times the diameter of the control.

4 When the quotient is considerably above 1.50, immunity to typhoid fever is suggested.

5 When it is considerably below this value nonimmunity is suggested.

When applied by statistical methods to groups of cases it may, however, be capable of much more definite interpretation as a qualitative index of typhoid immunity, since the general averages in this series of cases as well as in those previously reported by Gay and Force<sup>1</sup> show well-marked *average* differences in reaction between the immune and nonimmune.

It is suggested, furthermore, that when applied in this way to sufficiently large groups of cases, the typhoidin quotient may prove useful as a quantitative index of typhoid immunity.

For valuable assistance I am indebted to Dr. Ethel M. Watters and for criticisms and suggestions to my colleague, Dr. James L. Whitney.



# THE SPLENIC PATHOLOGY OF PERNICIOUS ANEMIA AND ALLIED CONDITIONS

A DUODENAL METHOD OF ESTIMATING HEMOLYSIS\*

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The spleen is dismissed with brevity in textbooks on pathology. Current medical literature fails to reveal a serious study of its histology, normal and pathologic.

In a close association with Professor Dr Hans Eppinger and his co-workers in the von Noorden clinic during the past year, I had opportunity to study not only the microscopic material obtained from that clinic, but in addition, many specimens loaned by Banti and Weidenreich.

The second part of this paper will deal with a study of the duodenal contents in a series of nineteen cases with a view of presenting a relatively simple yet accurate method of measuring the pleochromic and urobilinocholic so characteristic of the above splenic pathology.

## PART I

From Biermer's first definite and popular clinical conception of pernicious anemia in 1868 to Ehrlich's hematological studies in 1892, a host of workers contributed to the elucidation and confusion of this fatal malady. It was Syllaba in 1904 who first clearly recognized and properly emphasized the icteric feature of pernicious anemia.

In a demonstration of the splenic pathology of pernicious anemia, hemolytic icterus and hypertrophic cirrhosis, before the Society for Internal Medicine in Vienna in November, 1913, Eppinger gave the profession for the first time the results of many months of labor, suggesting what certainly amounted to an innovation, splenectomy for the first and last of the above conditions.

Prefacing his study of the pathologic picture in that most difficult and little understood organ with a survey of the normal histology as taught by Weidenreich, he pointed out the necessity of a proper schematic conception, to-wit:

Following the blood vessels as they traverse the trabecular partition, we find when a lumen of 0.2 mm is reached the artery leaves

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\* From the Department of Medicine, University of Minnesota.

\* Read before the Pathological Society, April 20, 1915.

the wall and penetrates a follicle. It is now known as the central artery, and is characterized by a fairly heavy wall. From this, laterally, spring numerous follicle capillaries of very delicate structure and first demonstrated in serial section by Weidenreich. These lose their identity in the margin of the follicle and the so-called pulp area. Following the central artery out from the follicle we have the pulp artery with its characteristic spindle-celled intima. This last portion now ends its existence as an artery in the so-called "Hulsen arteries" phase with its Schwaiger-Seidel wall. Via a capillary, phase communication is established with the venous sinus. This latter is generally accepted as practically a closed space, making up the bulk of the red pulp of the spleen. Lined with "*Stabzellen*," with their prominent nuclei, the basement membrane is probably very elastic, supported by ring fibers. The sinus empties by means of a vein, leaving the pulp and following the trabecular wall.

Experimental injection of the spleen via the artery seldom permits of filling of the sinuses. On the contrary, the injected material is seen to leave the artery in the peripheral zone of the follicle or the outlying pulp parenchyma. Foreign corpuscles introduced intravenously come to lie in this region.

A survey of a section from a spleen removed at operation in a case of pernicious anemia shows, contrary to what the organ findings in general would prepare one for, a great richness in blood, this richness limiting itself predominatingly to the pulp areas—the sinuses being comparatively empty.

All varieties of erythrocytes can be seen, and not infrequently is met the picture of engulfed cells in the macrophages in the sense of Dominici. A diapedesis of erythrocytes into the sinus is seen.

It now becomes pertinent to inquire as to the manner in which these great masses of erythrocytes get into the pulp area.

Physiologically, the central artery has thick walls. In a section through this artery in a spleen of pernicious anemia the arterial wall is, however, of enormous thickness. Characteristic is the media with its masses of inlaid hyalin. Prepared with Mallory's stain, this appears as a heavy mass of red-brown tint. In certain sections, filling the arterial wall almost to the point of complete obliteration, this degeneration feature extends out far into the pulp phase of the artery.

It is Eppinger's conception that this lumen-obliterating pathology works a hindrance to the normal blood stream in so far as to force an unusual amount of blood to travel via the capillaries directly into the pulp area. Once in contact with the connective tissue spaces of the pulp area, the erythrocyte is marked for destruction. It is a fact that the efferent artery of the follicle has a physiologic lumen rhythm,

controlled by the nerve supply, looking to the regulation of hemolysis, for Thoma found that he could best inject the sinuses via the artery with coloring matter when he added atropin. Contrary to the conception of Addis, hemolysis occurring to the extent of allowing the detection of free hemoglobin in the spleen is rare, and whether engulfed by the phagocytic endothelial cells or not, the actual hemolysis occurs in the Kupffer cells of the liver perienchyma.

In one of my illustrations from a case of hemolytic icterus is seen, as in pernicious anemia, a pulp area packed with erythrocytes, with the sinus space relatively empty.

In hypertrophic cirrhosis, so-called, the spleen presents to a less exquisite degree this hyperemia of the pulp and, on the contrary, a marked degree of fibroadenoma. This is properly regarded as an expression of a corrective tendency, for early in the life history of this type of cirrhosis during the acute catarrhal icterus attacks, the spleen presents a similar picture of acute hypersplenism.

## PART II

In animal experimentation the administration of a simple large dose of an hemolytic agent produces a passing change only in the total blood picture, so quickly does the vicarious activity of the bone marrow come into play. It is therefore not improbable that in human pathology the hemolytic factor is missed entirely until the activity of the bone marrow shows signs of failure.

Up to the present our safest means of arriving at some comprehension of the severity of the process has been the degree of immaturity of the elements in the blood stream. We have no adequate means of arriving at a valuation of the blood-destroying factor, and yet the blood-picture must of necessity be regarded as the sum total of the blood-destroying factor set against the blood-building factor. The fundamental factor is the former. The worth of this basic hemolytic factor we are now in a position to estimate in a quantitative study of the blood-derived pigment.

In the haunts of the liver-spleen circulation the erythrocyte is physiologically made *hors de combat*. The resulting hematin is metabolized into bilirubin in the liver parenchyma cell. In the bowel tract this latter is reduced after bacterial fashion into urobilinogen. A portion of this is lost in the stool, partly as the mother substance above and partly as urobilin. The greater part is returned to the liver via the portal system, there to be synthesized into bilirubin and possibly hemoglobin.

Eppinger, therefore, in his earlier work foresaw that the estimation of the urobilin stool output must yield a very valuable measure

of the hemolytic factor Applying the method evolved by Charmas he found normally an excretion per diem of 0.12 to 0.15 gm In cases of hemolytic icterus he postulated a higher total, but he was scarcely prepared for the enormous values found, 1.75 to 3.95 gm; namely, from fourteen to twenty-three times the normal In pernicious anemia 0.24 to 1.14 or two and a half to seven times normal values In anemia secondary to carcinoma, on the contrary, the values were around 0.012 or 1/10 normal In cases of hemolytic icterus and pernicious anemia, following splenectomy he found in both instances a reduction to from 0.015 to 0.062 gm per diem It was this similarity in hemolytic values as measured by the stool urobilin output that led Eppinger to have splenectomy performed in pernicious anemia, and to study more closely the pathology of the spleen so recovered For it may be remarked in passing that for microscopic study the surgically removed spleen, secured by tying off the artery first, is of value only as against the postmortem spleen where the final bone marrow exhaustion and depleting hemorrhages too completely overshadow the primary fulminating blood-destroying process

Working under Eppinger, Bondi began in 1913 a study of the blood derived pigments in duodenal contents removed with Einhorn's duodenal tube, applying the Charmas method for a measure of the urobilinocholie He argued that such estimations made, so to speak, at the very fountain-head of the pigment source must of necessity be less influenced by many factors working variations on the stool and urine output In general he found values running parallel with the stool findings, but, owing to the involved and not entirely accurate method of Charmas, he contented himself in most instances with a simple statement of the gross character of the bile and a qualitative test for urobilin and urobilinogen

Wilbur and Addis<sup>1</sup> in a very comprehensive and valuable study of the hemolytic values as found in the urinary and stool output came to the conclusion that of the two the latter gave promise of yielding the most fruitful help Using the spectroscopic method, it is their distinction to have emphasized the superiority of this method and the necessity of determining the value of urobilin and urobilinogen by the same standard, at the same time, in order to arrive at a correct worth of these very labile pigments

Stimulated by close association with the workers of the von Noorden clinic during the greater part of 1914 into the conviction that our knowledge of that fatal malady, pernicious anemia, was on the threshold of elucidation, the author on his return applied himself to the problem of adapting to the duodenal contents some method

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1 Wilbur and Addis THE ARCHIVES INT MED, 1914, xiii, 235

of estimating the bile pigments other than the time-consuming one of Charmas

In the method of Wilbur and Addis as applied to the urine the author found a simple, rapid and fairly accurate method for measuring the urobilinocholic. Since, however, the first expression of hemolysis is the pleochromic, it is of prime importance in the duodenal contents to estimate also, with some degree of accuracy, the bilirubin content. This is accomplished by the Huppert method, in so far as to allow of expressing the values secured, properly, as +, ++ or +++.

#### TECHNIC

Relative to the technic of securing the duodenal contents, a little needs to be said in the present state of diversity of methods. Contrary to the idea of certain workers, including Crohn and Rehfuess, it is not only not necessary to give food to secure secretion but distinctly undesirable. The mechanical stimulation of the metal bulb is all sufficient for secretory stimulation, and has the great advantage of enabling one to deal with undiluted, unmodified secretions. In the second place the capillary-sized tube is to be preferred over one of larger caliber, owing to the help secured by capillarity. At no time is it necessary or wise to apply suction. In the third place the time element is in favor of the above simple method in that it enables the securing of the contents in a remarkably short space of time—the average time consumed in arriving in the duodenum being twenty-five minutes.

The patient is prepared by allowing him to go food-free for twelve hours—an empty stomach is imperative. With the patient sitting, the bulb is placed on the posterior tongue, a swallow or two of water taken, and with puckered lips a sucking action is alternated with intervals of swallowing, teaching the patient at the same time the value of deep breathing to control nausea. Once the bulb has passed the cricoid ring level the disagreeable features are over. The further progress of the tube is largely beyond the control of patient and operator in that peristaltic action pulls the tube onward and the patient simply gives way to the tense tube by supplying more. On 80 cm. being reached the patient is placed on his right side close to the edge of the bed with hips elevated from 10 to 12 inches. This makes the pars pylorica the most dependent portion of the stomach. In from ten to thirty-five minutes the tube will have been carried into the duodenum and it now stands at 90 cm. If at any time the flow appears to be checked for an abnormally long time a few cubic centimeters of water are forced into it to dislodge the occluding particles. During this period it is necessary to test with red litmus the contents as it appears at the orifice of the tube each few minutes, for neither the required depth of tube nor a proper bile-colored contents are a sufficient guide as to the position of the tube. *It must react alkaline to litmus.* This alkaline-reacting portion is segregated, and after sufficient is secured for the work in hand the tube is removed and the contents immediately made use of in the following manner:

*1 Gross Appearance*—Color. This is of prime importance and four distinct shades are found. The chocolate-yellow secretion is characteristic of pleochromic. It always yields a +++ value bilirubin. The normal yellow bile may vary in opacity according as it is rich in bile acids admixed with hydrochloric acid. This is by many erroneously regarded as mucus. The lighter shade of yellow is significant of a duodenal secretion poor in biliary pigment, just as the colorless secretion is proof of absence of pigment.

*2 Bilirubin*—To 10 cc. of duodenal contents are added 10 cc. of an alkaline solution of calcium chlorid. After vigorous shaking this is filtered. The pre-

precipitate is dissolved under gentle heat in 10 cc of acid alcohol and the resulting green solution concentrated to a given volume. By colorimetric comparison with a standard green solution the quantity is indicated as +, ++, or +++.

3 *Urobilin and Urobilinogen*—To 10 cc of duodenal contents are added 10 cc of Schlesinger's solution, the whole thoroughly shaken and allowed to filter. The filtrate should be inclined to be slightly alkaline, if not, a drop or two of dilute ammonia solution are added. The filtrate will in the presence of urobilin show a more or less pronounced green opalescence. To 10 cc of this filtrate are added 1 cc of Ehrlich's benzaldehyd solution<sup>2</sup>. In the presence of urobilinogen a red color will develop. This is allowed to stand in a dark place for fifteen minutes, when it is subjected to a spectroscopic study for the values of both urobilin and urobilinogen. The acid character of Ehrlich's solution enhances the absorption bands of both these pigments many fold, the urobilinogen band being a very dense, narrow one in the yellow and the urobilin a wide one covering all of the blue into the green, the acid shifting the latter to the blue side.

The above solution is read in a graduate, and dilutions made with 95 per cent alcohol, until a point is reached for each pigment where the absorption band will have disappeared at a fixed median position of the aperture, to again reappear with two revolutions of the aperture towards closure<sup>3</sup>. The number

In developing this method as applied to the duodenal contents it would appear that bilirubin being so concentrated would present a practical difficulty in that it gives a diffuse absorption of the spectrum. Wilbur and Addis, working with the products of gallbladder fistulae, etc., made use of fullers' earth to remove bilirubin. I found that it did so but that it also removed especially urobilin. If the original 10 cc are well shaken with Schlesinger's solution before filtering, practically all of the bilirubin is removed, the retained quantity causing no error or inconvenience owing to the fact that the end-stages are read in a highly diluted medium where any slight diffuse absorption of the spectrum no longer operates.

That the above simple method is quite as accurate as one first removing bilirubin was established by comparing the values thus secured with those arrived at in which bilirubin was removed by the Huppert method prior to adding Schlesinger's solution.

After having arrived at a safe technic, the following studies were made, covering a total of nineteen cases during a period of five months.

#### MATERIAL EXAMINED

CASE 1—J A, Dec 15, 1914. Diagnosis pernicious anemia. Blood count, 1,000,000, hemoglobin, 22, index, 11, macrocytes, macroblasts. Duodenal tube introduced, 9 30. Opalescent, debris considerable, after fifteen minutes yellow tinge, negative to Congo throughout, total quantity of gastric secretion 60 cc. Total achylia, microscopic, spirals, polymorphonuclear cells with nuclei retained.

Entered duodenum at 9 50. Tube removed at 11 30. Total quantity 70 cc. Very dark chocolate yellow color, alkaline to litmus, microscopic negative. Bilirubin, + + +, urobilin, + + +, urobilinogen, + + +. Feces guaiac negative. Urine bilirubin, 0; urobilin, +.

<sup>2</sup> Paradimethylaminobenzaldehyd, 2 gm, acid hydrochloric, 15 cc, aq. dest., 15 cc.

<sup>3</sup> Kirchhoff and Bunsen, large model, page 12. of dilutions required for each element multiplied by twenty (5 cc of the original duodenal contents) will be the dilution value per 100 cc. Following the basis used by Wilbur and Addis, I have reduced the value to the scale of 1,000 cc.

Dec 30, 1914 Blood count, 930,000, hemoglobin, 25, index, 1.3, macrocytes, etc Duodenal tube introduced, 9 00 Opalescent, much debris, after ten minutes yellow, negative to Congo, total 35 cc, total achylia, microscopic, same as previous examination

Duodenum entered at 9 20 Tube removed at 11 00 Total quantity, 100 cc Exceedingly dark, alkaline to litmus, microscopic, negative Bilirubin, + + +, urobilin, 3,000, urobilinogen, 3,000 Total, 6,000 Urine bilirubin, 0, urobilin, 1,200

Jan 1, 1915 Blood count, 2,000,000, hemoglobin, 45, index, 1.2, resistance, 0.45-0.30 Duodenal tube introduced 9 35 Less debris, after ten minutes light yellow, negative to Congo, total 50 cc Tube removed 10 40 Dark yellow Bilirubin, + + +, urobilin, 2,000, urobilinogen, 3,600 Total, 5,600

Feb 25, 1915 Blood count, 2,400,000, hemoglobin, 54, index, 1.1, no blasts Duodenal tube introduced 9 20 Total 25 cc Duodenum entered at 9 45 Tube removed 10 40 Total 45 cc Less dark Bilirubin, + + +, urobilin, 1,600, urobilinogen, 2,000 Total, 3,600

March 20, 1915 Blood count, 2,600,000, hemoglobin, 60 Patient up in wheel chair Duodenal tube introduced 9 35 Ditto Total, 40 cc Duodenum entered at 9 55 Tube removed at 10 50 Total, 40 cc Dark yellow Bilirubin, + + +, urobilin, 1,400, urobilinogen, 1,600 Total, 3,000

CASE 2—E P Dec 26, 1914 Diagnosis secondary anemia<sup>4</sup> Blood count, 2,000,000, hemoglobin, 30, index, .75, anisocytosis and poikilocytosis Duodenal tube introduced 9 30 Milky secretion, much debris, after fifteen minutes yellow tinge Entered duodenum at 10 00 Tube removed, 11 00 Total quantity, 80 cc, light yellow, alkaline, microscopic cell debris, red blood cells Bilirubin, + +, urobilin, 1,000, urobilinogen, 0 Total, 1,000 Urine bilirubin, 0, urobilin, 0

CASE 3—J B Dec 18, 1914 Diagnosis ulcer ventriculi Blood count, etc, normal Duodenal tube introduced, 9 10, opalescent, later light yellow, Congo, +, total acidity, 39, total free, 29, free nuclei, sporing yeast Entered duodenum, 9 35 Tube removed at 10 20 Total, 50 cc, light yellow, opaque Bilirubin, + +, urobilin, 100, urobilinogen, 0 Total, 100

CASE 4—S H, Dec 26, 1914 Diagnosis pernicious anemia Blood count, 1,500,000, hemoglobin, 30, index, 1, macrocytes and macroblasts, leukocytes, 3,500 Duodenal tube introduced, 9 30 Opalescent, later yellow, Congo negative Entered duodenum, 10 10 Tube removed, 12 15 Total quantity, 60 cc Very dark chocolate yellow, alkaline Bilirubin, + + +, urobilin, 2,000, urobilinogen, 1,800 Total, 3,800<sup>5</sup>

CASE 5—M M Dec 26, 1914 Diagnosis gallbladder carcinoma<sup>6</sup> Blood normal Duodenal tube introduced, 10 00 Much debris, Congo positive, total acidity, 60, free acid, 40, total quantity, 60 cc, microscopic, no sarcinae or yeast Entered duodenum, 10 50, alkaline to litmus, milky, at no time yellow, total quantity, 35 cc Tube removed at 12 10 Bilirubin, 0, urobilin, 0, urobilinogen, 0 Total, 0

4 Postmortem eight months later revealed Laennec's cirrhosis with bleeding esophageal varices as the cause of the secondary anemia

5 After keeping duodenal contents in open flask exposed to room light for eight hours, urobilin value was found to be 1,800 and urobilinogen 1,000 Hence, while urobilinogen was being converted into urobilin, the latter was also disappearing into an unknown form After twenty-four hours all traces of both had disappeared

6 Postmortem examination four months later revealed adenocarcinoma, primary, of gallbladder with complete obstruction of common duct by direct extension

CASE 6—J F J Dec 29, 1914 Diagnosis secondary anemia Blood count, 2,500,000, hemoglobin, 17, index, 0.34, anisocytosis, poikilocytosis Duodenal tube introduced, 10 00 Milky, much debris, Congo positive Duodenum entered, 1 00, removed, 12 15 Quantity, 40 c c, light yellow Bilirubin, ++, urobilin, 0, urobilinogen, 0 Total, 0

CASE 7—Mr R Jan 5, 1915. Diagnosis ulcer ventriculi Blood not recorded Duodenal tube introduced, 9 35 Opalescent, after twenty-five minutes yellow tinge, quantity, 115 c c, Congo positive, total acidity, 60, free acid, 55, microscopic red blood cells, debris, no sarcinae Entered duodenum, 10 00 Tube removed, 11 00 Quantity, 80 c c; light yellow Opaque and stringy, alkaline at periods and again acid Bilirubin, ++, urobilin, 600, urobilinogen, 600 Total, 1,200

CASE 8—A R Jan 6, 1915 Laennec's cirrhosis Blood count, 4,700,000, hemoglobin, 85, index, 1— Duodenal tube introduced, 9 00 Much mucus, later yellow tinge, Congo plus Entered duodenum, 9 40 Tube removed, 10 40, quantity, 50 c c, faint yellow Bilirubin, +, urobilin, 1,000, urobilinogen, 0 Total, 1,000 Urine bilirubin, 0, urobilin, +

CASE 9—Miss M Jan 7, 1915 Vagotonia Blood negative Duodenal tube introduced, 9 15, much salivation, opalescent, later yellow, Congo plus, total acid, 50, free acid, 45 Total gastric secretion, 70 c c Entered duodenum, 9 45 Yellow and opaque, alkaline and acid alternating, total, 30 c c, tube removed, 10 05 Bilirubin, ++, urobilin, 200, urobilinogen, 0 Total, 200 Stool guaiac negative

CASE 10—J S Jan 11, 1915 Diagnosis gastric carcinoma Blood count, 1,900,000, hemoglobin, 37, index, 0.95, resistance, 0.45-0.25, normoblasts, megaloblasts Duodenal tube introduced, 9 30 Milky, much debris, later yellow tinge, quantity, 55 c c, Congo, negative, Wolff-Junghans, positive, 1-400 Entered duodenum, 9 50 Tube removed, 10 50 Total quantity, 60 c c, very light yellow Bilirubin, +, urobilin, 100, urobilinogen, 0 Total, 100 Stool light color, guaiac positive repeatedly on meat free diet

CASE 11—Mr E. Jan 13, 1915 Diagnosis hard liver Blood count, 4,500,000, hemoglobin, 70, leukocytes, 7,000, red cells chlorotic Duodenal tube introduced, 9 00 Milky, much debris, later yellow, Congo negative, total, 50 c c Entered duodenum, 9 20 Light yellow, alkaline Tube removed, 10 20, total, 30 c c Bilirubin, ++, urobilin, 100, urobilinogen, 0 Total, 100

CASE 12—Mrs E Jan 15, 1915 Diagnosis colloid goiter Blood not recorded Duodenal tube introduced, 8 40 Milky, much mucus, Congo negative, total, 50 c c Microscopic, shreds of epithelium Entered duodenum, 9 15 Removed, 10 00, total, 50 c c, light yellow Bilirubin, ++, urobilin, 0, urobilinogen, 0 Total, 0

CASE 13—Mr S Jan 19, 1915 Diagnosis Laennec's cirrhosis Blood count, 5,500,000, hemoglobin, 98, index, 1— Duodenal tube introduced, 9 00 Much debris, Congo negative, no Boas-Oppler bacilli Entered duodenum, 9 35, removed, 10 00, total, 85 c c, medium yellow, much debris Bilirubin, ++, urobilin, 1,200, urobilinogen, 0 Total, 1,200 Urine bilirubin, 0, urobilin, +

CASE 14—J C Jan 23, 1915 Diagnosis cardiac incompenation, luetic Blood count, normal Duodenal tube introduced at 9 20 Opalescent, later yellow, Congo positive, total acidity, 20 Entered duodenum, 9 45, normal yellow, alkaline, total in one hour, 50 c c Bilirubin ++, urobilin, 0, urobilinogen, 300 Total, 300 Urine bilirubin, 0, urobilinogen, 600

CASE 15—J H Feb 2, 1915 Diagnosis pernicious anemia Blood count, 1,100,000, hemoglobin, 27, index, 1.2, normoblasts Duodenal tube introduced, 9 40, first opalescent, much debris and shreds, later yellow tinged, Congo negative, total, 100 c c, no lactic Entered duodenum, 10 20, very



dark chocolate yellow, alkaline, total, 30 cc Microscopically bile casts Bilirubin, + + +, urobilin, 4,000, urobilinogen, 2,800 Total, 6,800 Urine bilirubin, 0, urobilin, 1,000

CASE 16—Mr H Feb 13, 1915 Diagnosis pernicious anemia Blood count, 1,200,000, hemoglobin, 26, index, 12, normoblasts Duodenal tube introduced, 9 15 Milky, much mucus, Congo negative Entered duodenum, 10 00, removed, 10 50, total, 50 cc, very dark yellow, alkaline Microscopically negative Bilirubin, + + +, urobilin, 2 000, urobilinogen, 1,200 Total, 3 200 Stool very rich in urobilinogen Urine bilirubin, 0, urobilin, 1,000

Feb 25, 1915 Blood count, 2,100,000, hemoglobin, 45, index, 1, no normoblasts Duodenal tube introduced, 9 25, Congo negative, etc, total, 35 cc Entered duodenum, 9 45, removed, 10 30, total, 40 cc, dark yellow Bilirubin, + + +, urobilin, 1,200, urobilinogen, 1,000 Total, 2,200 Urine urobilin +

TABLE OF TOTALS

No	Disease	Bilirubin	Urobilin	Uro- bilinogen	Total
1	Pernicious anemia	+ + +	+ + +	+ + +	+ + +
1	Pernicious anemia	+ + +	3,000	3,000	6,000
1	Pernicious anemia	+ + +	3,000	3 600	5 600
1	Pernicious anemia	+ + +	1,600	2 000	3,600
1	Pernicious anemia	+ + +	1,400	1,600	3,000
2	Secondary anemia	+ +	1,000	0	1 000
3	Ulcus ventriculi	+ +	100	0	100
4	Pernicious anemia	+ + +	2,000	1,800	3,800
5	Gall bladder carcinoma	0	0	0	0
6	Secondary anemia	+ +	0	0	0
7	Ulcus ventriculi	+ +	600	600	1,200
8	Laennec's cirrhosis	+	1,000	0	1,000
9	Vagotonia	+ +	200	0	200
10	Probable carcinoma	+	100	0	100
11	Liver path	+ +	100	0	100
12	Struma	+ +	0	0	0
13	Laennec's cirrhosis	+ +	1,200	0	1,200
14	Cardiac incompen- sation	+ +	0	300	300
15	Pernicious anemia	+ + +	4,000	2,800	6,800
16	Pernicious anemia	+ + +	2,000	1,200	3,200
	Pernicious anemia	+ + +	1,200	1,000	2,200
17	Mesarteritis syphi- litica	+ +	0	0	0
18	Vagotonia	+ +	100	0	100
19	Pernicious anemia	+ + +	2,300	2,500	4,800

CASE 17—Mr Nic C March 9, 1915 Diagnosis mesarteritis syphilitica Blood count, 6,000,000, hemoglobin, 83, chlorotic cells Duodenal tube introduced, 9 20, opalescent, later yellow, Congo plus, total acidity, 36, free acid, 32, total, 50 cc, no yeast or sarcinae Entered duodenum, 9 50, normal yellow, opaque, alkaline, total, 50 cc Bilirubin, + +, urobilin, 0, urobilinogen, 0 Total, 0

CASE 18—P A March 17, 1915 Diagnosis vagotonia Blood normal Duodenal tube introduced, 9 30, watery, later yellow, total, 85 cc, total acidity, 102, free, 80, free nuclei Duodenum entered, 10 30, opaque, yellow,

at times, only, alkaline, total, 60 c c Microscopic negative Bilirubin, ++, urobilin, 100, urobilinogen, 0 Total, 100

CASE 19—Mr W April 13, 1915 Diagnosis pernicious anemia Blood count, 1,300,000, hemoglobin, 30, index, 115, normoblasts and megaloblasts Duodenal tube introduced, 9 00, opalescent, later yellow, little debris, Congo negative, total, 60 c c Entered duodenum, 9 15, dark chocolate yellow tint, removed, 9 45, total, 30 c c Bilirubin, + + +, urobilin, 2,300, urobilinogen, 2,500 Total, 4,800 Urine urobilin, 1,000, urobilinogen, 100 Feces very rich in urobilinogen, guaiac, 0

#### SUMMARY

1 The early icteric feature of certain types of pernicious anemia is an expression of the primary fundamental hemolytic process of which the fully developed disease is a late bone-marrow exhaustion

2 Eppinger's hypothesis of hypersplenie furnishes a pathologic basis for the increased hemolysis Whatever the *causa causorum*, it must be regarded as established that it is through the instrumentality of the spleen that pathologic hemolysis is wrought

3 The excessive hemolysis of pernicious anemia is attended by both a pleochromie and urobilinochole

4 Pleochromie is an expression of the immediate hemolysis; urobilinochole of the heaped-up pigment in the portal system

5 Whether in a crisis or remission period, pleochromie is a constant finding This is in complete harmony with the fixed pathologic change in the spleen

6 Urobilinochole varies directly as the portal system is surcharged or becomes relatively empty of the plus of pigment It is highest in crisis regardless of whether or not gross liver changes can be demonstrated

7 Normally the duodenal secretion contains a certain level of bilirubin, occasionally urobilin, but never urobilinogen in considerable amounts

8 In anemia of chronic gastro-intestinal hemorrhage in which the blood picture may simulate genuine pernicious anemia, the duodenal estimation of bile pigments will definitely yield an absence of pleochromie and urobilinochole

9 The most constant blood finding in genuine pernicious anemia is the high index This is an expression of the overplus of hemoglobin-building material heaped up in the liver.

10 Essentially in both splenic anemia and in anemia of chronic gastro-intestinal hemorrhage, the process is one of abnormal blood loss, in the former the pigment moiety is saved to the organism, in the latter definitely and completely lost

# BLOOD UREA DETERMINATIONS IN 211 CASES<sup>†</sup>

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## LITERATURE REVIEW

Increased urea in the blood was first demonstrated in 1823 by Prevost and Dumas,<sup>1</sup> while working with nephrectomized animals Bostock,<sup>2</sup> in 1829, noticed an increase in the blood urea of certain albuminurics Richard Bright<sup>3</sup> with his co-workers—Prout, Babbington, and Christison (1836)—confirmed this observation and recognized it to be of clinical importance in nephritis Babbington and Christison also made estimations of urea in body fluids

Following the qualitative demonstration of blood urea, quantitative determinations were attempted by both French and German clinicians Picard<sup>4</sup> (1856) was the first to determine that the amount of blood urea varies with the nitrogen intake

Interest in the subject abated about this time, and for a period of forty years the references in the literature were infrequent Schondorff<sup>5</sup> (1899) revived the subject by an examination of the previous work, adding to it his own more accurate results, which confirmed the work of his predecessors He observed that the urea fraction of the total nonprotein nitrogen of the blood was variable Ascoli,<sup>6</sup> in 1901, using a precipitation method (acetic acid and sodium chlorid), and Strauss<sup>7</sup> (1902) with a similar method (heat and acetic acid), found that in cases of severe nephritis there was usually nitrogen accumulation He found a marked increase in the terminal state Muller<sup>8</sup> (1905) recognized urea retention to be of the highest value in diagnosing cases of uremia

F Widal and Javal<sup>9</sup> (1905) found that urea was retained in some cases of Bright's disease, and advocated a diminished protein diet in those cases

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<sup>†</sup> Submitted for publication July 21, 1915

1 Prevost and Dumas *Ann de chimie et de physique*, 1823, xxiii, 90

2 Bostock *Edinburg Med and Surg Jour*, 1829, xxxii, 28

3 Bright, Babbington, and Christison *Guy's Hosp Rep*, 1836, 1, 360

4 Picard *Thèse de Strassburg*, 1856

5 Schondorff *Arch f d ges Physiol (Pfluger's)*, 1899, lxxiv, 358

6 Ascoli *Pfluger's Arch f path Anat*, 1901, lxxvii, 103

7 Strauss *Die Chronische Nierentzündungen in ihrer Einwirkung auf die Blutflussigkeit und deren Behandlung*, Hirschwald, Berlin, 1902

8 Muller *Verhandl der deutsch path Gesellsch*, 1904-5, vii-ix, Supplement 80

9 Widal and Javal *Semaine méd*, 1905, xxv, 313

Von Noorden<sup>10</sup> (1907) obtained inconstant findings, but believed that the nitrogen accumulation in the blood constituted one of the most important phenomena of renal insufficiency

Obermayer and Popper<sup>11</sup> (1909) confirmed the results of previous workers, finding the incoagulable nitrogen higher in uremic cases than in normal cases, and emphasized especially the increase in the urea fraction They used heat and acetic acid for coagulation of blood proteins

Hohlweg<sup>12</sup> (1911) used acetic acid and monopotassium phosphate half saturated with sodium chlorid, to precipitate the blood proteins He found increased values in uremia, but found them also in other conditions While he considered nitrogen accumulation in the blood nonspecific of uremia, he thought it was of some prognostic value

Widal<sup>13</sup> (1911) using the hypobromite method, based a prognosis on the amount of urea per liter, patients with 1 to 2 gm per liter rarely live more than a year, with 2 to 3 gm only months or weeks, and with more than 3 gm a very short time This prognosis, however, he did not apply to cases with renal obstruction, where such obstruction could be removed, as here he found the urea dropped when the obstruction was relieved He found the retention was more permanent in chronic Bright's disease He believed the amount of blood urea was of definite value in the prognosis, especially of those cases difficult to determine from the clinical symptoms alone

Foster<sup>14</sup> (1912) using an alcohol precipitation and fractional separation method, found a considerable increase in nonprotein nitrogen in severe nephritis and in some other conditions When the total nitrogen reached 1 gm per liter, he regarded the prognosis as grave

Rowntree and Fitz<sup>15</sup> (1913) used the original Widal method in part of their determinations, but in the main they precipitated by the Widal method and then determined the nitrogen by the Kjeldahl method They reported the results obtained in fifty-seven cases No increase of blood urea was found in suspected nephritis (i e, clinically) In mild nephritis the average was 0.38 gm urea per liter, in cases of advanced nephritis 0.783 gm per liter, cases of cardiac decompensation without nephritis 0.70 gm per liter, and cardiac decompensation associated with nephritis 0.831 gm per liter In summarizing, they believed that the accumulation of nonprotein nitrogen in the blood of nephritics was of considerable prognostic value When

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10 Von Noorden *Metabolism and Practical Medicine*, 1907, 11, 486

11 Obermayer and Popper *Ztschr f klin Med*, 1911, lxxii, 332

12 Hohlweg *Deutsch Arch f klin Med*, 1912, civ, 216

13 Widal *Bull et mém Soc méd d hôp de Paris*, 1911, xxxii, 627

14 Foster *THE ARCHIVES INT MED*, 1912, x, 414

15 Rowntree and Fitz *THE ARCHIVES INT MED*, 1913, xi, 258

it occurred it was confirmatory evidence of renal insufficiency, whereas the absence of such increase was of less importance. As a point in differentiating cardiac and renal diseases they believed it was also of importance.

Frothingham, Fitz, Folin and Denis<sup>16</sup> (1913) found that the blood urea and the phenolsulphonephthalein excretion varied from normal in animals subjected to experimental uranium nephritis, and the amount of such variation agreed with the amount of kidney destruction. They observed a gradual increase in urea as nephritis developed and a gradual decrease as the kidney recovered. They concluded that the urea in the blood is a measure of the difference between the waste nitrogen urea produced in metabolism and the amount excreted in the urine. Such a retention of nitrogen in experimental nephritis was found also by Siegel,<sup>17</sup> Pearce, Hill and Eisenbrey,<sup>18</sup> Austin and Eisenbrey,<sup>19</sup> Folin, Karsner, Howard and Denis<sup>20</sup> and Mosenthal<sup>21</sup> (uranium, cantharidin, chromate, etc., nephritis). Mosenthal stated that there "Seems no doubt that kidney insufficiency in these cases is responsible for the retention." Karsner<sup>22</sup> also found retention in experimental arsenical nephritis, especially during the stage in which tubular destruction was most marked.

Soper and Granat<sup>23</sup> (1914) studied a series of ninety-seven cases, observing the urea content in spinal fluids. Their work will be referred to later under discussion of body fluids.

Folin, Denis and Seymour<sup>24</sup> (1914) reported a series of clinical experiments showing the relation of the nonprotein nitrogen and of the urea of the blood of nephritics to the amount of protein intake. Under low protein diet they were able to reduce the urea content from 0.67 gm per liter to practically a normal amount. They conclude that the rational means of determining protein tolerance is by determining the nonprotein nitrogen retention and not by blood pressure findings. They found no connection between nitrogen retention and blood pressure as had previously been described by Strauss, who believed that the high blood pressure of nephritics is frequently associated with nitrogen retention.

16 Frothingham, Fitz, Folin, and Denis. *THE ARCHIVES INT MED*, 1913, xii, 245.

17 Siegel. *Ztschr f exper Path u Therap*, 1907, iv, 561.

18 Pearce, Hill, and Eisenbrey. *Jour Exper Med*, 1910, xii, 196.

19 Austin and Eisenbrey. *Jour Exper Med*, 1911, xiv, 366.

20 Folin, Karsner, Howard, and Denis. *Jour Exper Med*, 1912, xvi, 789.

21 Mosenthal. *THE ARCHIVES INT MED*, 1914, xiv, 844.

22 Karsner and Denis. *Jour Exper Med*, 1914, xix, 63.

23 Soper and Granat. *THE ARCHIVES INT MED*, 1914, xiii, 131.

24 Folin, Denis, and Seymour. *THE ARCHIVES INT MED*, 1914, xiii, 224.

Agnew<sup>25</sup> (1914), using the method of Folin and Denis,<sup>26</sup> found in the majority of cases of nephritis, when the excretion of phenolsulphonaphthalein was below 40 per cent, there was an increase in the nonprotein blood nitrogen and in the blood urea. This did not hold true in cases of cardiac decompensation. He found the incoagulable nitrogen determinations valuable in the diagnosis of incipient uremia, coma, and in conjunction with phenolsulphonaphthalein in cardiorenal diseases.

Frothingham and Smilie<sup>27</sup> (1914), using the method of Folin and Denis, found many cases of chronic nephritis with normal nonprotein nitrogen in the blood. Cases showing 0.35 gm per liter were clinically more severe than the cases with no retention, while the cases with 0.5 gm or over were clinically of still more severe type. No nonnephritic cases showed nitrogen retention. They found that the excretion of phenolsulphonaphthalein varied inversely with the retention of nitrogen, except in cases of cardiac decompensation. Blood pressure and pulse pressure they believed to be of less prognostic value than nitrogen retention.

Tileston and Comfort<sup>28</sup> (1914), following the technic of Folin and Denis, observed a large series of cases (142). Their most important deduction was that in chronic nephritis without uremia the urea values were normal or moderately elevated. Cases of uremia showed great increase without exception. The excretion of phenolsulphonaphthalein was proportional to the nitrogen retention. Outside of uremia, extremely large urea values, over 1 gm per liter, were encountered only in severe anemias and intestinal obstruction. They found retention in chronic plumbism, lobar pneumonia, syphilis (36 per cent of cases), diabetes with coma, and acute yellow atrophy of the liver. Normal values were obtained in eclampsia, chronic passive congestion, compensated valvular lesions, pericarditis, endocarditis, acute rheumatism, uncomplicated scarlatina, cerebral hemorrhage, functional nerve diseases, diabetes without coma, myxedema, exophthalmic goiter, and malignant disease. They believed the estimation of nitrogen to be of the greatest value in the diagnosis of uremia and also in the prognosis of chronic nephritis. They thought that the total nitrogen was of more prognostic importance than the urea nitrogen.

Ovsiannikova<sup>29</sup> (1914) found a mortality of 18 per cent in cases of chronic nephritis with blood urea below 0.5 gm per liter, 18 per

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25 Agnew. *THE ARCHIVES INT MED*, 1914, xiii, 485.

26 Folin and Denis: *Jour Biol Chem*, 1913, xiv, 29.

27 Frothingham and Smilie. *THE ARCHIVES INT MED*, 1914, xiv, 541.

28 Tileston and Comfort. *THE ARCHIVES INT MED*, 1914, xiv, 620.

29 Ovsiannikova. *Russk Vrach*, 1914, xiii, 253.

cent for 0.5 to 1 gm per liter, 58 per cent for 1 to 2 gm per liter, and 85 per cent for 2 to 5 gm per liter.

Widal, Weill and Radot<sup>30</sup> (1914) found that the phenolsulphone-phthalein test and the urea in the blood serum ran parallel. They rose and fell together in normal cases and in cases of Bright's disease. The mere estimation of the urea content of the blood from time to time they believed to be a reliable and accurate index of the azotemia. In chronic kidney disease when the urea was less than 0.5 gm per liter there was no question of azotemia, when 1 gm, they believed the test should be frequently repeated, when 2 gm, the prognosis was bad.

TABLE 1—NORMAL

Number	Age	Blood Pressure	Phthalein, Per Cent	Blood Urea	
				Two Hours After Meals	Seventeen Hours Fasting
38	23	100	72	0.163	.
39	21	102	87	0.163	0.120
40	21	122	67	0.156	0.156
41	21	122	82	0.120	
43	20			0.160	
47	24	116		0.102	
58	22	100	67	0.102	
11	36	112	70	0.180	0.132
69	21	110		..	0.108
77	23		65	0.160	
82	21	.	42	0.220	
83	23	126	60	0.216	
176	25	122	82	0.252	. .
195	20	120	50	0.204	
196	26	132	65	0.108	
197	22	120	70	0.120	

Farr and Krumbhaar<sup>31</sup> (1914) stated that in cirrhosis of the liver the total nitrogen was increased only in cases accompanied by definite nephritis. They did not support the view held by Morel and Mouriquand,<sup>32</sup> and by some other investigators, that in destructive diseases of the liver the percentage of urea to the total nitrogen was decreased, to the contrary, they found that the percentage of urea remained normal.

<sup>30</sup> Widal, Weill, and Radot. *Presse méd.*, 1914, xxii, 565.

<sup>31</sup> Farr and Krumbhaar. *Jour. Am. Med. Assn.*, 1914, lxiii, 2214.

<sup>32</sup> Morel and Mouriquand. *Bull. et mém. Soc. méd. d'hôp. de Paris*, 1913, xxxv, 266.

Mosenthal<sup>21</sup> (1915), in a series of interesting experiments, was able to produce in dogs experimental uranium nephritis of two types. In nephritis of moderate severity there was an increase in nitrogen elimination. This increase he demonstrated experimentally to be due, not to any previous retention, but to an increased protein catabolism. The more severe cases showed a decreased elimination of nitrogen in the urine with a true nitrogen retention due to kidney insufficiency. He also showed that a gain or loss of water in the body was a factor that influenced the quantitative estimations of nonprotein nitrogen in the blood.

Foster<sup>33</sup> (1915) observed a series of cases of severe cardiac decompensation without nephritis, and found in them an increase in the nonprotein nitrogen averaging 0.6 gm per liter. In four of these cases necropsy substantiated the clinical findings. The nonprotein nitrogen in chronic parenchymatous he found lower than in chronic interstitial nephritis. In general, he found the most pronounced nitrogen increase in cases with high arterial pressure. He states that uremia may occur when the nitrogen is low, that is, no higher than in a latent nephritis. The convulsive type of uremia showed a nitrogen content double that of the asthenic type. A high nonprotein nitrogen in the absence of uremic symptoms he believed to be of more definite prognostic value than in the presence of uremic symptoms, while a normal finding did not exclude a remotely fatal issue.

Rowntree, Marshall, and Baetjer<sup>34</sup> (1915) also reported two cases of myocardial insufficiency with necropsies showing no kidney changes except chronic passive congestion. Clinically, both showed urea retention, 0.67 and 1.1 gm per liter, respectively.

#### TECHNIC

We have used in this series of experiments the urease method of Marshall,<sup>35</sup> fully described by the author.

#### BLOOD UREA IN NORMAL CASES

The several observers have obtained widely varying values for the normal blood urea, largely due to the method employed. A glance at Table 2 will show this clearly.

Our observations cover a series of sixteen cases, all persons in apparently perfect physical condition. The urine in each case was normal. The average amount of blood urea obtained after seventeen hours fasting was 0.129 gm per liter. Two and one-half hours after

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33 Foster. *THE ARCHIVES INT. MED.*, 1915, xv, 356.

34 Rowntree, Marshall, and Baetjer. *THE ARCHIVES INT. MED.*, 1915, xv, 543.

35 Marshall. *Jour. Biol. Chem.*, 1913, xiv, 283, *ibid.*, 1913, xv, 487.



TABLE 2—NORMALS OF VARIOUS AUTHORS

Gm per Liter	Authors	Method
0.20 to 0.41	Foster	Alcoholic precipitation and fractional separation
0.30 to 0.50	Rowntree and Fitz	Widal hypobromite and Kjeldahl
0.61	Schondorff (quoted by Agnew)	Phosphotungstic acid precipitation
0.10 to 0.20	Strauss (quoted by Agnew)	Heat and acetic acid
0.23 to 0.28	von Jaksch <sup>37</sup>	Phosphotungstic acid precipitation
0.18	Obermayer and Popper	Heat and acetic acid
0.31	Hohlweg	Dilute acid, 5 per cent monopotassium phosphate and one-half saturated sodium chloride
0.11 to 0.14	Folin and Denis	Precipitation with methyl alcohol, then with zinc chloride, hydrolyzed, Ness
0.21	Aszacki <sup>38</sup>	derived, and colorimetry
0.08 to 0.25	Farr and Austin <sup>39</sup>	Uranium acetate
0.43	Farr and Austin (quoted by Hinman)	
0.30 to 0.50	Widal	Hypobromite method
0.12 to 0.14 (2½ hours)	Tilleston and Comfort	Technic of Folin and Denis
0.13 to 0.20 (12 hours)	Tilleston and Comfort	Technic of Folin and Denis
0.05 to 0.07 (fasting)	Picard	Precipitation with alcohol and then Liebig's titration method
0.11 to 0.13 (after food)	Picard	
0.50	Weill, Vallery and Radot <sup>40</sup> (quoted by Hinman)	

37 Von Jaksch Leyden Festschr, 1902, 1, 197

38 Aszacki Ztschr f klin Med, 1913, lxxvii, 1

39 Farr and Austin Jour Exper Med, 1913, xviii, 228

40 Widal, Weill, Vallery, and Radot Jour d'Urol, 1913, v, 68

a heavy protein meal this was increased to 0.175 gm per liter, or an average increase of 0.046 gm per liter. Reference to Table 1 will show that the values obtained varied from 0.108 gm per liter to 0.252 gm. per liter, in no case reaching 0.300 gm per liter. The average per cent of phenolsulphonephthalein excreted in two hours was 68

#### RELATION OF PROTEIN INTAKE

That the amount of protein ingested had a distinct bearing on the quantity of blood urea, was observed by Picard in 1856. He found also that the time for taking blood for examination, with reference to food intake, caused certain variations. These observations have been repeatedly confirmed and emphasized by different authors.

Case 80, of our own observation, demonstrates this very clearly. A normal individual, with a phenolsulphonephthalein excretion of 60 per cent, had a blood urea of 0.326 gm per liter. She gives a history of being a heavy meat eater. On a low protein diet for a period of three days the blood urea dropped to 0.168 gm per liter, later, on a moderate protein diet the value increased to 0.240 gm per liter. In nephritics, who have been given a low protein diet, we have also observed a drop in the blood urea (Case 56). The practical value of giving a low protein diet to decrease the nonprotein nitrogen in the blood of nephritics, has been recently demonstrated by various authors (Folin, Denis and Seymour, Tileston and Comfort, etc.).

#### CAUSES OF BLOOD UREA INCREASE

The finding of a normal as well as an increased amount of urea in nephritics, along with the fact that there is increased urea in numerous pathological conditions, in which no clinical or pathological evidence of nephritis exists, leads us to the conclusion that blood urea increase cannot be explained by renal insufficiency alone. Faulty kidney excretion, resulting in true nitrogen retention, is no doubt the chief factor in cases of nephritis, but many other cases cannot be explained on the basis of retention. We observe in some cases involving general metabolism, without any evidence of nephritis, an increased blood urea. Cases of exophthalmic goiter show a moderate increase. In one case we observed still greater increase during a condition of hyperthyroidism following a partial gland resection. This increase dropped to normal simultaneously with the improvement of the patient.

Whether increased protein catabolism alone explains these cases is difficult to state. There may be an abnormal urea combination in the blood, which makes elimination by the kidney impossible, as has been suggested by Mosenthal.

2	29	Puerperal septice- mia	Acute toxic nephritis	Spec	1 022	M A	Pos	Blood casts Many hy, gran and blood casts	137	65	0 120 1 380	Recovery Died two days later
6	48	Lobar pneumonia	Acute toxic nephritis	Spec		L A	Pos					
12	55	Acute bowel ob- struction	Acute toxic nephritis	900	1 016	M A	Neg	Gran and hy casts	118		0 180	Died one day later Fourth day of disease
34	54	Lobar pneumonia	Acute toxic nephritis						104		0 660	Fourth-day of dis- ease
36	44	Lobar pneumonia	Acute toxic nephritis	Spec	1 016	S A	Pos	Occ gran cast			0 264	Third day
42	24	Lobar pneumonia	Acute toxic nephritis	Spec	1 030	S A	Neg	Hy and gran casts			0 288	Fifth day
52	21	Lobar pneumonia	Acute toxic nephritis	Spec	1 022	T	Neg	Occ gran cast, Occ W B C			0 396	Died Fifth day
54	34	Lobar pneumonia	Acute toxic nephritis	Spec	1 022	M A	Neg	Many hy casts	108	37	0 340	Second day
60	22	Pregnancy (5 mo ) Appendicitis	Acute toxic nephritis	600 1,500	1 012 1 007	M A S A	Neg Neg	Few W B C Many W B C Many W B C Occ hy cast	126	10	0 180 0 264	Recovery 3/10 3/20
71	55	Lobar pneumonia	Acute toxic nephritis	Spec	1 018	T	Neg	Few gran casts	99	22	0 624	Died same day
73	39	Lobar pneumonia	Acute toxic nephritis	Spec	1 022	T	Neg	Few gran and hy casts, few W B C	110	37	0 420	Second day after onset
87	43	Lobar pneumonia	Acute toxic nephritis	Spec	1 022	T	Neg	Occ W B C	91	42	0 384	Fourth day after onset
95	27	Acute parenchy- matous	Acute toxic nephritis	Spec	1 022	M A		Many gran and hy casts, Occ W B C	120	27	0 740	
106	28	Lobar pneumonia	Acute toxic nephritis	Spec	1 007	M A	Pos	Few hy casts, R B C	90	55	0 700	Sixth day
115	8	Primary anemia	Acute toxic nephritis	Spec	1 022	L A		Hy casts, few W B C	92	T	0 797	Died two days later
121	32	Acute pulmonary tuberculosis	Acute toxic nephritis	Spec	1 020	S A	Neg	Occ hy and gran casts, Occ W B C	110	T	0 600	Died next day
122	43	Lobar pneumonia	Acute toxic nephritis	Spec					112	C 2	0 156	Ninth day
144	39	Common duct ob- struction	Acute toxic nephritis	Spec	1 018	T		Many hy and gran casts	125	15	1 510 1 740	Ble in urine 5/10 5/11
151	37	Lobar pneumonia	Acute toxic nephritis	Spec	1 014 1 023	T T	Pos	Occ hy cast Occ W B C		20	0 606 0 103	Sugar trace 5/29 6/2
156	32	Acute parenchy- matous	Acute toxic nephritis	Spec	1 023	M A	Neg	Num hy casts	110	25	0 144 0 680	Died Fourth day same day 5/15
				Spec	1 015	M A	Pos	Few hy casts W B C and R B C	134	26	0 720	
				1,000	1 008	M A	Pos	Gran and hy casts			0 912	5/19
				Spec	1 008	T	Pos	Hy and gran casts, W B C	140	20	0 776 0 672	5/22 5/25
				Spec	1 018	T	Pos	Hy and cellular casts, R B C and W B C		75	0 76	5/31 Left hospital in fair condition
163	30	Lobar pneumonia	Acute toxic nephritis	Spec	1 017	S A	Neg	Occ hy cast, Num W B C	112	64	0 144	Third day same day
175	25	Lobar pneumonia	Acute toxic nephritis	Spec	1 025	T	Pos	W B C and R B C	100	50	0 56	Second day
178	39	Lobar pneumonia	Acute toxic nephritis	Spec	1 018	T	Neg	Hy and gran casts, W B C		63	0 572	Fourth day next day
181	42	Lobar pneumonia	Acute toxic nephritis	Spec		T	Neg	Occ hy cast, Occ W B C	140	70	0 650	Fourth day
187	50	Meningitis	Acute toxic nephritis	Spec	1 016	M A	Pos	Occ W B C, many gran casts		T	0 784	Fourth day six hours later

Cases of acute infection often present the same picture. Here there is undoubtedly increased catabolism along with the elevation of temperature. It seems quite probable that an abnormal urea compound, as well as an absolute increase in the amount of urea nitrogen formed, combined with kidney insufficiency of varying degree, occurs in the terminal state.

That pure circulatory disturbance may give rise to increase in blood urea has been demonstrated in cases of cardiac decompensation, where necropsy showed the absence of kidney lesions (Foster).

Another factor which has to be considered is the percentage of water in the body fluids. In cases of persistent vomiting, esophageal stenosis, acute hemorrhage, etc., we have observed an increase in the blood urea, and conversely, in a case of high blood urea, we have observed a distinct drop following the addition of a considerable quantity of water to the body fluids. Concentration of and dilution of the blood probably account in part at least for these phenomena.

#### UREA IN PATHOLOGICAL CONDITIONS

In studying various pathological conditions we have considered a blood urea above 0.250 gm per liter as abnormal. For purposes of classification we have divided the cases into clinical groups, including (1) acute nephritis, (2) suspected chronic nephritis, (3) mild chronic nephritis, (4) advanced chronic nephritis, (5) advanced chronic nephritis with cardiac decompensation, (6) miscellaneous genito-urinary, (7) diseases of heart, (8) anemias, (9) acute infections, (10) chronic infections, (11) diabetes mellitus, (12) diseases of thyroid, (13) malignancy, (14) miscellaneous cases.

#### ACUTE NEPHRITIS

Twenty-five cases of acute nephritis were observed. Of these eighteen were toxic nephritis accompanying lobar pneumonia. The urea averaged 0.578 gm per liter, thus showing a definite increase. Only three cases showed a normal amount of urea. All showed albumin and casts in the urine. Twenty-two phthalein tests were made, sixteen showed decreased elimination.

Case 12 of intestinal obstruction following operation showed normal urea before operation. With developing obstruction, many hyaline and granular casts, with a large amount of albumin, appeared in the urine. The blood urea was 1.390 gm two days before death.

Cases 95 and 156 were acute parenchymatous nephritis of no determined etiology. Case 156 entered the hospital the third day of illness, complaining of weakness and headache. His previous history was entirely negative. He showed a medium amount of albumin, casts,

TABLE 4—SUSPECTED CHRONIC NEPHRITIS

No	Age	Diagnosis	Kidney	Urine				Blood Pressure	Phthalic acid, per Cent	Blood Urea	Remarks
				Quant., cc	Sp Gr	Alb	Blood				
3	50	Arteriosclerosis	Arteriosclerotic	Spec	1 020	T		230		0 096	Hypert thyroidism
				Spec	1 026	T				0 115	
7	72	Cystitis	Chronic interstitial nephritis	Spec	1 005	T	Pos	130		0 084	
8	54	Headache	Chronic interstitial nephritis	Spec	1 008	T		135		0 210	
46	55	Prostatic hypertrophy	Chronic interstitial nephritis	Spec	1 004	S T		190		0 258	
50	67	Suspected chronic nephritis		1,500	1 012	S T		122	77	0 288	
101	55	Suspected chronic nephritis		1,800	1 015	S T		120	65	0 264	
102	35	Edema		Spec		S T		170		0 376	
105	47	Suspected nephrolithiasis		Spec		S A	Pos	150	70	0 212	4/21 B P 115 of 140 1 day in bed 7/14
114	60	Arteriosclerosis		400	1 015	S T		110	65	0 546	
127	65	Prostatic hypertrophy		Spec	1 023	S T		134	72	0 040	
132	46	Suspected chronic nephritis		700	1 009	T		110	65	0 152	Dyspnea Edema
174	67	Hemorrhage, retinal		Spec	1 016	S T	Pos	155		0 264	

white and red blood cells, a phthalein of 26 per cent, and urea of 0.720 gm per liter. A few days later the urea rose to 0.912 gm per liter. With improvement in symptoms the urea fell promptly and phthalein elimination increased to normal.

Case 144 was common duct obstruction. When the patient entered the hospital she showed blood urea of 1.512 gm per liter, with 13 per cent phthalein excretion. The common duct opened spontaneously and at the same time the accompanying nephritis began to clear. The urea and phthalein promptly returned to normal.

These cases followed practically the same course observed by the various investigators of acute experimental nephritis.

#### SUSPECTED CHRONIC NEPHRITIS

Twelve cases which were clinically suspected of being nephritis, showed an average urea of 0.248 gm per liter, which is a normal value. The phthalein excretion was normal on all the cases which were examined. Reference to Table 4 will show the details of each case.

#### MILD CHRONIC NEPHRITIS

Table 5 shows the results in the nineteen cases of mild chronic nephritis. Of these five were parenchymatous and fourteen were interstitial nephritis. The average blood urea was 0.288 gm per liter. Five of the cases showed normal blood urea. The phthalein excretion in this group was, with one exception, normal.

#### ADVANCED CHRONIC NEPHRITIS

Sixteen cases of advanced chronic nephritis came under our observation. The average blood urea of these cases was 0.444 gm per liter. Three cases showed normal values.

Two cases of albuminuric retinitis associated with chronic parenchymatous nephritis were observed. It is interesting to note that both of these cases showed a normal urea. Widal has stated that albuminuric retinitis is always associated with azotemia. Tileston and Comfort had one case which also showed a normal urea value, but in the cases of long standing eye symptoms the urea was increased. Both of the cases coming under our observation were of brief duration, as far as the retinitis was concerned. It is of interest to note that in one case with a urea of 0.180 gm per liter the excretion of phthalein was but 15 per cent.

One case of uremia was observed. This was of transitory character, following a prostatectomy. The maximum urea at the time the patient had uremic symptoms was 1.008 gm per liter, with but a trace of phthalein excreted. This case is also of interest, because

TABLE 5—MILD CHRONIC NEPHRITIS

No	Age	Diagnosis	Kidney	Urine				Blood Pressure	Phthal- ein, per Cent	Blood Urea	Remarks
				Quan, cc	Sp Gr	Alb	Blood				
49	53	Diabetes mellitus	Chronic parenchyma- tous nephritis Chronic interstitial nephritis	1,400	1.016	T		173		0.242	2 per cent sugar No sugar on 60 gm white bread per day
20	57			Spec	1.030 1.012	T T		151		0.150	
10	54	Cystitis	Chronic interstitial nephritis	Spec	1.003	T		154	70	0.276	
44	56	Prostatic hyper- trophy	Chronic interstitial nephritis	1,300	1.003	T		180	75	0.163	
64	24	Post nephrectomy	Chronic interstitial nephritis	Spec	1.005	S T		123	50	0.264	
75	80	Prostatic hyper- trophy	Chronic interstitial nephritis	Spec	1.012	M A	Pos	137	T	0.293	Cystitis
123	45	Chronic pulmon- ary tuberculosis	Chronic parenchyma- tous nephritis	Spec	1.023	T		100	87	0.283	Iritis
135	40	Syphilis		Spec	1.020	T	Pos	115		0.312	
133	35	Syphilis	Chronic interstitial nephritis	Spec	1.011	S T		112		0.112	
136	33	Syphilis	Chronic parenchyma- tous nephritis	Spec	1.017	T		102	77	0.430	
171	54	Syphilis	Chronic interstitial nephritis	Spec	1.015	T		170		0.120	
149	50	Tabes dorsalis	Chronic interstitial nephritis	Spec	1.010	T		110		0.112	
153	54	Arteriosclerosis	Chronic interstitial nephritis	Spec	1.003	S T		150		0.264	Menopause
180	34	Secondary anemia	Chronic interstitial nephritis	2,500	1.004	S A		110	62	0.264	
132	60	Chronic pulmon- ary tuberculosis		Spec	1.022	T		85	80	0.372	
133	42	Chronic interstitial nephritis		Spec	1.003	S T		173	67	0.204	
192	25	Chronic pulmon- ary tuberculosis		200	1.010	T				0.150	
202	54	Diabetes mellitus	Chronic interstitial nephritis	2,320	1.030	T		212	65	0.200	5 per cent sugar
186	40	Chronic antrum infection	Chronic parenchyma- tous nephritis	Spec	1.020	S A				0.312	

TABLE 6—ADVANCED CHRONIC NEPHRITIS

No	Age	Diagnosis	Kidney	Urine			Blood Pressure	Phthal- ein, per Cent	Blood Urea	Remarks
				Quan, cc	Sp Gr	Alb				
4	78	Prostatic hypertrophy	Chronic interstitial nephritis	1,400	1 015	S T			1 008	2/8
5	26	Abortion	Chronic parenchymatous nephritis	Spec	1 016	L A	Pos	220	0 156	1/24 Before abortion
		Albuminuric retinitis		Spec	1 010	L A	Pos	190	0 180	1/26 Post abortion
				Spec	1 010	L A	Pos	190	0 180	1/28
				Spec	1 016	M A	Neg	250	0 144	1/31
15	27	Albuminuric retinitis	Chronic parenchymatous nephritis	Spec	1 016	L A	Pos	220	0 228	2/22 Retinitis still marked
16	33	Chronic parenchymatous nephritis		Spec	1 005	S A	Pos	154	0 324	12/30
				Spec	1 008	T	Pos	230	0 276	1/7 Patient in fair condition
18	55	Chronic interstitial nephritis		Spec	1 002	T	Neg			1/8
22	16	Chronic parenchymatous nephritis		Spec	1 015	L A	Pos		0 319	3/2
23	33	Chronic interstitial nephritis		Spec	1 003	M A	Pos	150	0 372	4 months' duration
				2,800	1 006	T	Neg	134	0 408	2/9 History of scarlet fever and syphilis
48	51	Diabetes mellitus	Chronic interstitial nephritis	5,500	1 010	S T				Mercurial treatment
				480	1 025	T		168	0 144	Limited fluids to 1,500 cc and gave 20 gm NaCl in 24 hours
51	51	Chronic parenchymatous nephritis		750	1 015	T				2/28 Diabetes four years' duration
56	63	Chronic interstitial nephritis		1,200	1 012	M A	Pos			2 5 per cent sugar
76	29	Chronic parenchymatous nephritis		Spec	1 016	M A	Neg	240		3/1 0 5 per cent sugar
118	52	Chronic interstitial nephritis		Spec	1 015	M A	Neg	180	0 480	8/5 Suspected nephrolithiasis
				Spec	1 014	L A		250	0 210	3/14
134	17	Chronic interstitial nephritis		Spec	1 013	T	Neg	170	0 414	3/7
172	53	Diabetes mellitus	Chronic interstitial nephritis	2,200	1 033	M A			0 384	3/13 Six days' rest in bed
184	42	Diabetes mellitus	Chronic interstitial nephritis	Spec	1 010	L A	Pos	163	0 396	Has mild edema, cardiac hypertrophy and pyorrhea
				Spec	1 015	M A	Neg		0 276	Cardiac hypertrophy, mild edema, anemia, hematuria three years ago
				Spec	1 015	M A	Neg		1 080	Edema, ascites, dyspnea
				Spec	1 033	M A			0 362	One year's duration Obesity
				Spec	1 033	M A				Gangrene 13 per cent sugar
				Spec	1 015	M A			0 336	Diabetic and acetone
				Spec	1 033	M A		150		Sugar-free on carbohydrate-free diet
								75		6/1 5 per cent sugar



TABLE 7—ADVANCED CHRONIC NEPHRITIS WITH CARDIAC DECOMPENSATION

No	Age	Diagnosis	Kidney	Urine				Blood Pressure	Phthalic acid, per Cent	Blood Urea	Remarks
				Quan, cc	Sp Gr	Alb	Blood				
1	75	Bronchitis Myocarditis	Arteriosclerotic	400 800	1 022 1 018	M A T	Pos	190	15	0 518 0 604	1/14 1/20 Died 1/23/15
139	62	Myocarditis Alcoholic cirrhosis	Chronic parenchymatous nephritis	200	1 019	S A	Pos	135	T	0 453	5/5 Cyanosis Dyspnea
141	54	Syphilis	Chronic interstitial nephritis	Spec	1 023	M A				0 763	5/12 Pelliculum B P 120 two years ago Death 5/20/15
143	69	Arteriosclerosis Myocarditis	Arteriosclerotic	Spec	1 015	S T		170		0 120 0 713 0 159	Pulvis alternans
152	62	Myocarditis	Chronic interstitial nephritis	Spec	1 030	S A		185	T	0 285	Dyspnea Aortic dilatation Large heart
161	56	Arteriosclerosis Myocarditis	Arteriosclerotic	Spec	1 014	T		242		0 266	Edema Dyspnea

TABLE 8—MISCELLANEOUS GENITO-URINARY CASES

No	Age	Diagnosis	Kidney	Urine				Blood Pressure	Phthal- ein, per Cent	Blood Urea	Remarks
				Quan, cc	Sp Gr	Alb	Blood				
4	78	Prostatic hypertrophy Cystitis Acute retention	Chronic interstitial nephritis	Spec	1 004	S A	Pos				
10	54	Cystitis						190	20	0 194	1/20 Before operation 1/21 One day before operation 1/30 Three days after operation 2/4 Hiccough, drowsiness 2/7 Symptoms of uremia
20	28	Pyelonephritis	Chronic interstitial nephritis	Spec	1 008	T	Neg			0 306 0 864	2/8 2/11 2/19 2/26 3/10 4/12 4/13 Patient went home 1/30 Old nephritic abscess calcified, drained 1 month before operation
14	54	Prostatic hypertrophy	Large right kidney	500	1 014	T	Neg			0 360	Two days before operation
15	56	Hydrocele	Chronic interstitial nephritis	1,300	1 003	T	Neg			0 354	
51	54	Suspected nephro- lithiasis	Negative	Spec	1 020	T	Neg			0 108	
64	24	Post nephrectomy	Chronic parenchymatous nephritis	1,200	1 012	M A	Pos			0 108	
68	50	Pyonephrosis	Mild chronic nephritis	500	1 005	S T				0 276	
75	80	Prostatic hypertrophy		200	1 018	T	Pos			0 336	
97	53	Nephrolithiasis	Mild chronic nephritis	Spec	1 016	T				0 168	
99	34	Pyelitis		Spec	1 012	M A	Pos			0 340	
				500	1 022	S T				0 480 0 210	
										3/5/15 3/14	
										0 264	Nephrectomy four months previously, one half of horseshoe kidney removed
										0 360 0 516	3/18 3/30 Two days post nephrectomy
										0 300 0 264	4/10 5/1
										0 264 0 264 0 334 0 393 0 414 0 444	3/23 4/7 1/26 4/13 4/23
										0 336	Operation 3/31
										0 312	One day after thyroidectomy 4/26 Five days after thyroidectomy Marked tetany

No	Age	Diagnosis	Kidney	Blood Pressure	Hematin, Per Cent	Blood Urea	Remarks
26	22	Double mitral	Negative	130		0.252	Old history of rheumatism Compensation good
33	17	Double mitral	Negative	100	75	0.324	Severe tonsillitis and arthritis Compensation good
63	60	Double mitral	Negative	167	72	0.180	Mild decompensation
109	47	Myocarditis Pleurisy Relative mitral insufficiency	Negative	142	82	0.180	Mild decompensation
158	56	Myocarditis (mild)	Negative	120		0.276	Dyspnea Chronic cough Edema of feet Mild decompensation
165	64	Myocarditis	Negative	162	63	0.163	Marked edema of feet Mild decompensation
188	45	Myocarditis	Negative	130		0.180	Cardiac asthma
193	45	Myocarditis	Negative	103	70	0.300	Dyspnea
107	45	Myocarditis	Negative	102		0.336	Wassermann two plus Dyspnea
201	45	Double mitral	Negative	120		0.204	
203	63	Myocarditis	Negative	163		0.380	Heart markedly dilated Gastric distress

TABLE 10—ANEMIAS

No	Age	Diagnosis	Kidney	R B C Per c mm	Hem Per Cent	W B C Per c mm	Blood Pressure	Phthalin, Per Cent	Blood Urea	Remarks
31	60	Primary anemia	Negative	1,910,000	45	6,100	119	67	0.135	One year duration
115	8	Primary anemia	Parenchymatous nephritis Alb Med Amt Blood Hy casts	1,300,000	24	19,400	92		0.577	Six weeks' duration Two days before death
132	14	Primary anemia	Negative	550,000	14	3,000	110		1.773	Blood, heart } 6 hours p m
27	26	Secondary anemia	Negative	2,340,000	40	16,100	80		1.030	Pericardial fluid
173	46	Secondary anemia	Negative	2,950,000	35	8,000	118		0.245	Functional heart murmur Anemia six months' duration
180	34	Secondary anemia	Chronic Interstitial nephritis Sp Gr 1.001 Alb small amt Occ hy. cast	2,700,000	20	6,200	140	62	0.163	Acute hemorrhage from puncture wound of back
185	38	Secondary anemia	Negative	2,730,000	35	6,000	150		0.200	Acute hemorrhage from fibroid uterus Two weeks' duration
									0.264	Fibroid uterus Hemorrhage over period of four years
									0.103	Fibroid uterus. Hemorrhage over a period of three years

of the progressive decrease of blood urea to normal, while the phthalein excretion remained small (9 per cent)

That a high urea can occur without uremic symptoms is shown in Case 134. This case of chronic interstitial nephritis had a blood urea of 1.080 gm per liter.

One case of diabetic coma with chronic interstitial nephritis had 2.340 gm per liter, probably as a terminal condition.

The cases on which a phthalein test was made practically all show a distinct decrease along with the rise in blood urea.

#### ADVANCED CHRONIC NEPHRITIS WITH CARDIAC DECOMPENSATION

The average blood urea in this series of cases was 0.523 gm per liter, which is higher than the same group of cases without cardiac decompensation, and also distinctly increased above normal value. The blood pressure of all these patients was distinctly elevated. The phthalein was just a trace in two cases, 15 per cent in another case. Two of the cases with the highest blood urea (0.694 and 0.768 gm per liter) died shortly after the test was made. Case 141 with a urea of 0.768 gm per liter was in a fairly good physical condition at time of observation. No normal values were obtained in this group of cases.

#### MISCELLANEOUS GENITO-URINARY CASES

Twelve miscellaneous cases have been recorded under Table 8. Three cases of prostatic hypertrophy were observed, each having a definite nephritis. One case showed a normal value; the others were increased. Case 4 is interesting in that it shows a rise of blood urea from 0.194 to 0.864 gm per liter associated with a partial urinary retention progressing to a complete retention. After operation the patient had typical uremic symptoms with a blood urea of 1.008 gm per liter. As the patient improved the blood urea dropped progressively until a normal value was reached (0.108 gm per liter). The patient was in fairly good condition at this time.

We found increased urea in cases of nephrolithiasis, pyelonephritis, and pyonephrosis, cystitis, and pyelitis. The cystitis was complicated with chronic interstitial nephritis.

We had under observation a very interesting case of polycystic kidneys (Case 108). Both kidneys were markedly enlarged, the excretion of phthalein was practically nil, and the patient was suffering from chronic uremia. The blood urea was 3.360 gm per liter, which is the highest value we have obtained in any case. It is remarkable in that the patient is living, three months after the urea examination was made.

## DISEASES OF THE HEART

Four cases of double mitral lesions were observed. Three showed normal blood urea. One case had a severe tonsillitis and arthritis and showed a slight increase in blood urea (0.321 gm. per liter). Four of the seven cases of myocarditis were slightly elevated. In no case did the blood urea increase to 0.400 gm. per liter.

## ANEMIAS

Rowntree and Fitz (1913) report a case of splenic anemia with polyserositis with a blood urea of 0.280 gm. per liter.

Tileston and Comfort (1914) obtained normal or only slightly raised blood ureas in two cases of secondary anemia due to hemorrhage and in one case of Banti's disease. In two cases of hemolytic anemia they found marked retention, 0.597 and 0.790 gm. per liter.

We have studied three cases of hemolytic anemia (primary) and four of secondary anemia due to hemorrhage. Two of the cases of secondary anemia had a normal blood urea, the other two cases showed only a mild increase. Two cases of chronic pernicious anemia showed 0.456 gm. and 0.255 gm. per liter, respectively. Case 115 was a very acute pernicious anemia in a child, terminating fatally in six weeks. Two days before death the blood urea was 0.597 gm. per liter, six hours postmortem the urea in heart's blood was 1.778 gm. per liter. He developed a terminal nephritis with many hyaline and blood casts.

## LOBAR PNEUMONIA

Tileston and Comfort (1914) report blood ureas on fourteen cases of lobar pneumonia. The highest value was 0.360 gm. per liter, the lowest 0.112 gm. per liter. They believed there was no relation between retention and prognosis. Foster (1915) found a rise in non-protein nitrogen in lobar pneumonia exceptional and associated only with marked circulatory disturbance.

We made forty-two blood urea determinations on twenty cases of lobar pneumonia. These ranged from 0.120 gm. per liter to 1.044 gm. per liter, with an average of 0.405 gm. per liter. In thirty-six of the areas the values were higher than normal, many of the cases showed a rather marked increase. Some of these patients were cyanosed at the time blood was taken but a number were not. Seventeen of the twenty cases ran a definite toxic nephritis, which probably helped to increase the blood urea. Only one case with a urea of over 0.6 gm. per liter recovered. We believe that in cases with marked increase a bad prognosis should be given. We found in cases of recovery the maximum increase was about the time of crisis, but most of our cases even on the first and second day after onset showed some urea retention. For more details the reader is referred to Table 11.

TABLE 11—LOBAR PNEUMONIA

No	Age	Day of Disease	Complications	Blood Pressure	Phthal- ein, Per Cent	Blood Urea	Remarks
0	48		Toxic nephritis . . . . .	137	65	0 120	Temperature 105 F Recovered
34	54	4th	Acute toxic nephritis	118		0 480	Temperature 104 F Died next day
36	44	4th	Acute toxic nephritis	104		0 660	Temperature 105 F Died next day
42	24	3d	Mild acute toxic nephritis			0 264	Temperature 104 F Prompt recovery
		5th	Mild acute toxic nephritis			0 288	Nephritis cleared up
52	21	8th	Mild acute toxic nephritis			0 396	Temperature 105 F Died one day later
54	34	1st 5th 8th 10th 11th	Acute toxic nephritis plus syphilis	108		0 540 0 276 0 540 0 220 0 156	Temperature 105 F. Crisis ninth day Recovery
59	34	2d	Negative	92	67	0 156	Temperature 103 F Recovery
71	55	7th	Mild acute toxic nephritis	99	22	0 624	Temperature 105 F Died one day later
73	30	1st 2d 4th 6th	Severe acute toxic nephritis	110	37	0 384 0 420 0 372 0 300	Temperature 103 F
							Afebrile
87	43	4th 7th 12th 15th	Mild acute toxic nephritis	94 115		0 384 0 228 0 344 0 180	Temperature 105 F Afebrile Afebrile Recovery
106	28	4th 6th 9th	Mild acute toxic nephritis	88 90	55	0 180 0 300 0 156	Temperature 104 F Recovery
120	47	5th 9th 16th 20th	Mild acute toxic nephritis	112	62	0 360 0 456 0 408 0 300	Temperature 103 F Afebrile Recovery Afebrile Recovery
151	37	2d 4th	Severe acute toxic nephritis	110 110	38	0 300 0 660	Temperature 105 F Temperature 105 F Died on fourth day
163	30	3d	Acute toxic nephritis	112	64	0 444	Temperature 105 F Died one day later
164	09	5th 7th	Negative	100 110	63	0 420 0 336	Temperature 104 F Recovery
169	40	2d 4th 8th	Negative	108	78	0 336 0 516 1 011	Temperature 105 F Marked cyanosis Died on tenth day
	05	2d	Mild acute toxic nephritis	100	80	0 336	Temperature 105 F

TABLE 12—SEPTICEMIA

No	Age	Diagnosis	Kidney	Blood Pressure	Phthal- ein, Per Cent	Blood Urea	Remarks
2	29	Puerperal septicemia (streptococcus)	Acute toxic nephritis			0.924	Death next day
70	28	Streptococcus septicemia Knee infection	Acute toxic nephritis	110	24	0.132 0.516 0.348 0.240 0.303 0.180 0.120	3/19/15 2/20/15 3/24/15 3/20/15 4/ 1/15 4/ 8/15 4/10/15 Died two days later from acute hemorrhage due to perforation of vessel 4/9/15 Died ten hours later, six days after operation
93	16	Streptococcus peritonitis from operation	Negative previous to operation			1.272	

TABLE 13—MENINGITIS

No	Age	Diagnosis	Kidney	Blood Pressure	Blood Urea	Urea Spinal Fluid	Remarks
110	51	Streptococcus meningitis from otitis media	Negative	63	0.703		Patient died seven hours later. Urinstoid operation day before
126	35	Streptococcus meningitis from otitis media	Occult blood, otherwise negative	115	0.370	0.24	Died next day. Streptococcus found in spinal fluid
130	53	Acute meningitis ? Meningococcus	Negative	115	0.223	0.225 0.150 0.120	5/ 4/15 175 cells per cc in spinal fluid 5/11/15 W. B. C. 20,000, phthalein test 5/20/15 75 cells per cc
187	50	Streptococcus meningitis	Acute parenchymatous nephritis		0.284	0.75	10 p. m. 4 p. m. Phthalein, trace only, Carbuncle 1 p. m. died at 5 p. m.

## SEPTICEMIA

A single case of puerperal sepsis with recovery we find reported in the literature by Tileston and Comfort, with a normal blood urea

Three cases of streptococcic septicemia came under our observation, all terminating fatally. Two of these patients developed severe acute toxic nephritis. The urine was not obtained from the third.

In Case 2 of puerperal septicemia the patient had a blood urea of 0.924 gm per liter, and died within twenty-four hours; Case 93, general peritonitis, a patient with a blood urea of 1.272, died within ten hours, Case 70 had a blood urea of 0.516 gm per liter on March 20, 1915, which dropped progressively to 0.120 gm per liter on April 10, 1915, when the patient died from acute hemorrhage.

## MENINGITIS

Three cases of streptococcic meningitis and one case of meningococcic meningitis were observed. The three cases of streptococcic meningitis showed definite increase in the urea, that of meningococcic meningitis showed normal urea (Table 13).

## ROCKY MOUNTAIN SPOTTED FEVER

Only one case of spotted fever was observed. This was in a patient on the sixth day after onset, with marked petechial eruption, mild delirium and cyanosis. The blood showed 0.690 gm of urea per liter. At the time there was only a trace of albumin in the urine. The patient died two days later.

TABLE 14—ROCKY MOUNTAIN SPOTTED FEVER

No	Age	Urine	Blood Urea	Remarks
154	17	Trace albumin	0.690	Died two days later

## SYPHILIS

Folin and Denis in 1913 reported sixty-three cases. Of these 46 per cent showed a moderate elevation in blood urea.

Tileston and Comfort (1914) observed eleven cases. Approximately 50 per cent showed increase of blood urea. They found albumin and casts in practically all of their cases, and concluded that the kidney was affected in a considerable percentage of syphilitics. Nitrogen retention was more evident in the tertiary stage, according to their observation.

Thirty-nine cases of demonstrable syphilis and four cases of clinically suspected syphilis are included in our series and the results are recorded in Table 15.



TABLE 15—SYPHILIS

No	Age	Kidney	Blood Pressure	Phthal ein, Per Cent	Blood Urea	Stage	Special Symptoms	Wassermann	Remarks
171	18	Negative	140		0.103	1	Primary on lip	++	No treatment
206	34	Negative	132		0.360	1		—	Primary three days
119	28	Negative	118		0.141	2		++	Six salvarsans and mercury
124	24	Negative	155		0.264	2		++++	Three salvarsans and mercury
129	33		130		0.360	2	Ulcer tongue	++++	No treatment Two years' duration
135	40	Mild parenchymatous nephritis	118		0.312	2	Iritis	++	Little treatment
138	35	Mild chronic interstitial nephritis	112		0.242	Late 2		+	Infection ten years ago Well treated then
141	54	Chronic interstitial nephritis	170		0.420 0.763	Late 2	Pain	—	Primary twenty one years ago Little treatment
142	35	Negative	105		0.283	Early 2	Adenitis	++	Three salvarsans and mercury
145	30	Negative	120		0.306	2	Rectal syphilids	++	No treatment
146	28	Negative	118		0.276	2	None	+	Four salvarsans
155	34	Negative	135		0.210	2	None	++	Primary eight years ago Treatment three years
166	22		144		0.225	2	Mucous patches, mouth and rectum	++	Primary eight months ago No treatment
170	32	Negative	120		0.120	2	Maculopapular eruption	++	Five salvarsans and mercury for eight months
179	28	Negative			0.350	2	No symptoms now	—	No treatment
21	41	Negative	120		0.222	3	Ulcer nasal septum	++	Four salvarsans and mercury for four months
67	40	Negative	148		0.155	3	Ulcer of palate and perforation	++	No treatment
88	28	Negative	122		0.150	3	Perforation palate	++	No treatment
89	25	Negative	115		0.180	3	Pain in legs	++	No treatment
92	27	Negative	117	70	0.330	3	Hoarseness	++	No treatment
94	40	Negative			0.240	3	Iritis Opaque vitreous	++	Two salvarsans two months previously
98	25	Negative			0.204	3	Acute anisocoria	+	
103	30	Negative	126		0.162	3	Six miscarriages	++++	No treatment
104	35	Negative	142		0.204	3	Acute diplopia	++	No treatment

107	45	Negative	102	45	0 336	3	Myocarditis	++	No treatment
111	30	Negative			0 360	3	Diplopia	++	Little treatment four years ago
113	26	Negative	145		0 324	3	Gumma of clavicle	+++++	No treatment
136	33	Chronic parenchymatous nephritis	162	77	0 480	3	Laryngismus stridulus	++	Three salvarsans and mercury
136	33	Chronic parenchymatous nephritis			0 360	3	Laryngismus stridulus	+++++	Three salvarsans and mercury
117	25	Negative			0 264	3	Iritis	+++++	No treatment
157	45	Negative	142		0 348	3	Extra ocular paralysis	++	No treatment
162	24	Negative	120		0 240	3	Facial paralysis	+	Four salvarsans and mercury
190	45	Negative	140	90	0 256	3	Anisocoria Fixed pupils	+++++	Treatment sixteen years ago
199	42	Negative	172		0 180	3	Girdle pain	++	Two salvarsans and mercury
200	32	Negative	120		0 216	3	Leukoplakia	+++++	Two salvarsans four years ago
204	60	Negative	132		0 216	3	Reflexes increased	++	Six salvarsans
23	35	Negative	116		0 300	Paresis	Hyper K K Mental deterioration	+++++	No treatment
125	40	Negative			0 204	Paresis	Argyll Robertson pupils	+++++	No treatment
149	50	Chronic interstitial nephritis	140		0 312	Tabes	Absent K K Argyll Robertson pupils	+++++	No treatment
198	41	Negative	120		0 276	Tabes	Lightning pains	+++++	No treatment
							Diplopia Absent K K Argyll Robertson pupils	+++++	No treatment
							Adenitis (T.B.) Hem 40%		

TABLE 16—SUSPECTED SYPHILIS

No	Age	Kidney	Blood Pressure	Phthal cin. Per Cent	Blood Urea	Spinal Fluid	Stage	Special Symptoms	Remarks
84	42	Negative	150	60	0 312	0 324	3	Cerebrospinal	Perforated septum Arteriosclerosis Wassermann negative
79	57	Negative	130		0 228	0 238	3	Cerebrospinal Arcus senilis	Wassermann negative in blood and spinal fluid Two cells per cmm spinal fluid
68	45	Negative			0 114	0 120	3	Vertigo Gastric disturbances	Wassermann negative in blood and spinal fluid
205	"	Negative	128		0 210		3	External strabismus Diplopia	Wassermann negative

Two cases were primary lues and one of these showed an increase in blood urea. Neither case showed any evidence of kidney pathology.

There were thirteen cases in the secondary stage. Eight showed an elevation of blood urea (i. e., above 0.250). Three of these had a distinct nephritis. Five cases showed an increase above 0.300 gm per liter, four of whom had practically no treatment for their syphilis.

Twenty cases of the tertiary stage were studied. Eight of these showed an increased urea. But two cases had evidence of a distinct nephritis. Four of the five patients in whom the urea was over 0.300 gm per liter had received no treatment.

Paresis and tabes dorsalis were each observed in two instances. The urea was elevated in one paralytic and in both cases of tabes. One case of tabes had an interstitial nephritis.

#### SUMMARY

To summarize our observations:

1. Twenty of the thirty-nine cases showed an elevated blood urea (approximately 50 per cent), of the primary stage 50 per cent, secondary 62 per cent, tertiary 40 per cent, and quaternary 75 per cent.

2. But six cases had evidence of a nephritis.

3. Nearly 80 per cent of the thirteen cases in whom the blood urea was over 0.300 gm per liter had received no treatment.

4. No relation between the Wassermann test and the amount of blood urea can be drawn.

5. The highest urea was 0.768, a patient who had acquired syphilis twenty years ago, and has now a chronic interstitial nephritis.

6. It is interesting to note that of the cases who received three or more salvarsans, but one was increased above 0.300 gm per liter.

#### PULMONARY TUBERCULOSIS

A glance at Table 17 will show that in two cases out of seven, there was an increase in blood urea. Case 121, an acute miliary tuberculosis, with a severe acute toxic nephritis, had 0.600 gm urea per liter, and terminated fatally. Case 123, a chronic advanced tuberculosis, was slightly raised (0.288 gm per liter), and had a mild parenchymatous nephritis. Other authors have observed retention in cases of tuberculosis (Tileston and Comfort).

#### DIABETES MELLITUS

Seven cases of diabetes mellitus are included in our series (see Table 18). Five of these were complicated with chronic nephritis. Three of the cases showed definite increase in blood urea. They were all cases with nephritis. Case 184 had urea 0.336 gm per liter on admission to the hospital. Two days later he developed coma and had a blood urea of 2.340 gm per liter. He died the following day.

TABLE 17—PULMONARY TUBERCULOSIS

No	Age	Stage of Disease	Kidney	Blood Pressure	Phthal- ein, Per Cent	Blood Urea	Remarks
24	40	Mild chronic	Negative				
121	32	Acute millary	Acute toxic nephritis	120	45	0 150	Twenty years' duration
123	45	Chronic advanced	Mild parenchymatous ne- phritis	110	T	0 600	Temperature 103 F Died
168	50	Chronic advanced	Negative	100~	87	0 288	
192	25	Chronic advanced	Mild parenchymatous ne- phritis	104		0 132	Temperature 100 F Syphilis compl
209	35	Chronic	Negative	145		0 120	
						0 180	Marked ascites two weeks' duration Tu- berculous peritonitis Temp 102 F

TABLE 18—DIABETES MELLITUS

No	Age	Sugar, Per Cent	Diabetic Acetone	Kidney	Blood Pressure	Phthal- ein, Per Cent	Blood Urea	Remarks
0	13	5						
11	51	Neg	Present	Negative	130	.	0 204	
20	57	T	Negative	Negative	180		0 120	
18	51	2	Negative	Negative	154		0 162	Carbohydrate free diet
170	51	0 5	Negative	Mild chronic interstitial nephritis	168	55	0 150	Sugar free on 60 gm white bread
181	53	1 3	Negative	Chronic interstitial nephritis	.		0 141	Four years' duration
192	5	5	Present	Chronic interstitial nephritis	150	75	0 362	Gangrene foot
202	51	5	Present	Chronic interstitial nephritis	150	.	0 336	Mild arteriosclero
			Present	Chronic interstitial nephritis	212	63	2 310	In coma Died on following day
				Chronic interstitial nephritis			0 300	

TABLE 19—DISEASES OF THYROID

No	Age	Diagnosis	Kidney	Blood Pressure	Phthalic acid, Per Cent	Blood Urea	Remarks
72	20	Exophthalmic goiter	Negative	120	82	0.264 0.324 0.180	Before operation 3/23/15 Shortly after operation 3/30/15 After operation 4/5/15
65	32	Exophthalmic goiter	Negative	110	74	0.240 0.114 0.120	Before operation 3/15/15 After operation 3/20/15 After operation (leaving hospital) 3/30/15
30	32	Exophthalmic goiter	Negative	135	55	0.276	Before operation
3	50	Hypothyroidism Arteriosclerosis	Arteriosclerotic kidney	250		0.096 0.119	
160	31	Colloid goiter	Negative	170		0.504	Having thyroid extract treatment for six months Weakness, dyspnea and tachycardia

TABLE 20—MALIGNANCY

No	Age	Diagnosis	Kidney	Blood Pressure	Blood Urea	Urea Fluid	Remarks
55	60	Recurrent papilloma of ovary	Negative		0.262	0.426 0.450	Aceltic Palpable abdominal mass
90	28	Malignant pleura		176			
91	40	Adenocarcinoma stomach	Mild parenchymatous nephritis		0.204	0.240	Aceltic Jaundice
128	50	Extensive sarcoma of face	Negative	150	0.273		Taken just before death
150	53	Adenocarcinoma stomach	Negative	115	0.649		Wascularity
207	50	Sarcoma of hip	Negative	160	0.408		Before operation Persistent vomiting Before operation

TABLE 21 — MISCELLANEOUS

No	Age	Diagnosis	Kidney	Blood Pressure	Phthal em, Per Cent	Blood Urea	Fluid Urea	Remarks
12	55	Acute obstruction (malignant)	Acute toxic nephritis			1 380		Died one day later Indeanuria
13	29	Acute obstruction (? etiology)	Negative			0 336 1 080 0 714		2/1/15 Condition good 2/5/15 After operation 2/6/15 Died two days later
17	46	Acute obstruction Incarcerated hernia	Negative	115		0 360 0 246		2/ 5/15 Six days after operation Recovery
25	26	Psoriasis	Negative	123		0 168		Chronic
53	23	Urticaria				0 336		First day of rash
81	33	Pityriasis rosea	Negative	125		0 216		Fourth day of rash
61	21	Second degree burn (steam)	Negative			0 132	0 108	Two days' duration
100	45	Second degree burn (gas)	Negative			0 288	0 242	Three days' duration
19	38	Fractured skull	Negative Glucose T	110		0 284 0 300		2/ 8/15 One day after injury 2/11/15 No coma
96	16	Cerebral hemorrhage	Alb L A	190 260		0 306		Blood pressure raised 70 mm in 2 hours Death five hours after hemorrhage
116	28	Concussion	Negative	156		0 426 0 336		Patient comatose Fourteen days later, conscious
78	54	Gout	Negative	130	67	0 288		
144	39	Obstruction common duct (postoperative)	Alb T Many casts Alb T Occ hy east	125 132	13 20 56	1 512 1 560 0 636 0 168 0 144		5/10 Complete obstruction 5/11 Vomiting, not severe 5/14 Duet opens 5/20 6/ 2
179	51	Obstruction common duct (postoperative) 1 pplepsy	Negative (bile)		60	0 408		Jaundice
62	39		Negative	108		0 156		Attack grand mal day previous
27	56	Traumatic pleurisy	Negative	150	T	0 354 0 186		General anasarca, marked edema 0 540 pleuritic fluid urea Died four days later
112	23	Lophagelial stenosis Gunshot wound	Negative	88		2 268 2 316		Gastrostomy done six days previously Marked anemia Died same day urea was taken
140	46	Intracranial tumor	Negative	132 145		0 210		Choked disk extra ocular palsy, head ache Wassermann negative Marked Comatose three days later
145	24	Chronic arthritis	Negative	122		0 276		
143	54	Arteriosclerosis				0 394		Menopause
167	23	Bone cyst (jaw)	Arteriosclerotic Necrotic	190		0 264		
		Neurasthenia						

## DISEASES OF THE THYROID

We made blood urea determinations on three cases of exophthalmic goiter. All showed a urea slightly above normal before operation. Following operation the urea dropped to normal. We studied only one case of myxedema. The patient had in addition marked arteriosclerosis. Two determinations of urea were made, both of which were slightly below normal.

Case 160 was a patient with a large colloid goiter who had taken thyroid extract for six months. He showed marked hyperthyroidism. His blood urea was increased to 0.504 gm per liter.

The phenolsulphonaphthalein output in all three cases of exophthalmic goiter was normal or slightly increased in amount.

## MALIGNANCY

A series of six cases was studied, the results of which are shown in Table 20. Two cases show slight increase. Cases 150 and 207 show a distinct elevation, 0.648 and 0.408 gm per liter, respectively. Neither case had any clinical evidence of nephritis. This observation is not in accord with the conclusion of Tileston and Comfort, who stated that no changes were met with in malignant disease which could not be ascribed to a complicating renal disease.

## MISCELLANEOUS

We have studied twenty-four miscellaneous conditions. Four cases of intestinal obstruction had an increased blood urea. Cases 12 and 13 showed very high values, 1.380 and 1.080 gm per liter, respectively. One case of obstructed bile duct, complicated with parenchymatous nephritis, showed 1.560 gm per liter, but dropped promptly to normal as soon as the obstruction was relieved. Case 112 gave marked urea increase, 2.311 gm per liter. The patient had an esophageal stenosis.

Slightly raised values were found in urticaria, fracture of the skull, cerebral hemorrhage, cerebral concussion, traumatic pleurisy, bone cyst, arteriosclerosis, and chronic arthritis. Normal values were obtained in psoriasis, pityriasis rosea, epilepsy, and a functional neurosis.

## THE UREA CONTENT OF BODY FLUIDS

A most excellent summary of the literature on the subject is included in the work of Soper and Granat (1914). To that article the reader is referred.

Soper and Granat studied the urea content in the spinal fluid in ninety-seven cases. They found that the amount of the urea in the spinal fluid usually agreed with that in the blood. Most of the variations were due to the difference in time of taking of the fluids.

TABLE 22—UREA CONTENT IN BODY FLUIDS

No	Diagnosis	Fluid	Fluid Urea	Blood Urea
51	Chronic nephritis .. .	Spinal .	0 166	0 210
84	? Syphilis . . .	Spinal . . .	0 324	0 312
74	Paresis . . .	Spinal . . .	0 270	
54	Syphilis . . .	Spinal . . .	0 390	0 540
79	Syphilis .	Spinal	0 253	0 223
66	Syphilis . . .	Spinal . .	0 120	0 114
125	Paresis . . .	Spinal . . .	0 204	0 193
126	Meningitis . . .	Spinal . . .	0 324	0 370
130	Meningitis . . .	Spinal .	0 255	0 283
140	? Brain tumor	Spinal .	0 204	0 240
130	Meningitis .	Spinal . .	0 180	.
162	Cerebrospinal syphilis	Spinal	0 193	0 210
130	Meningitis . . .	Spinal . .	0 120	.
183	Chronic nephritis . . .	Spinal .	0 240	0 204
187	Meningitis .	Spinal .	0 793	0 384
191	Chronic nephritis	Spinal	0 596	0 396
198	Tabes dorsalis	Spinal .	0 264	0 276
89	Syphilis	Spinal	0 216	0 180
210	Bulbar paralysis	Spinal	0 120	
55	Ovarian tumor (malignant).	Peritoneal	0 426	0 262
91	Carcinoma of stomach .	Peritoneal .	0 204	
91	Carcinoma of stomach . .	Peritoneal . .	0 253	
91	Carcinoma of stomach	Peritoneal . . .	0 348	
55	Ovarian tumor. . . .	Peritoneal	0 480	.
209	Tubercular peritonitis	Peritoneal	0 180	0 180
57	Ovarian tumor	Cyst .	0 432	0 223
131	Ovarian tumor . .	Cyst	0 216	0 192
137	Ovarian tumor	Cyst	0 163	0 156
45	Hydrocele		0 276	0 340
120	Hydrocele .		0 484	
61	Second degree burn . .	Vesicle	0 103	0 132
100	Second degree burn .	Vesicle. . .	0 242	0 253
27	Pleurisy . . . .	Pleural .	0 540	0 483
90	Malignant pleura . . .	Pleural . .	0 240	0 204
115	Anemia . . . .	Pericardial	1 650	1 773
211	Gonorrheal arthritis . . .	Joint fluid	0 240	0 240



TABLE 23—PHTHALEINS

Case Number	Per Cent. Phthalein 2 Hrs	Blood Urea	Case Number	Per Cent Phthalein 2 Hrs	Blood Urea
196	65	0 108	202	65	0 309
41	82	0 120	29	70	0 306
6	65	0 120	84	60	0 112
197	70	0 120	100	57	0 312
40	67	0 156	89	60	0 126
59	67	0 156	33	75	0 324
137	82	0 156	85	42	0 124
77	65	0 160	114	80	0 324
165	68	0 168	92	70	0 325
144	56	0 168	107	45	0 326
38	72	0 168	110	67	0 130
30	87	0 168	169	75	0 336
44	75	0 168	175	80	0 336
48	55	0 144	160	75	0 326
5	15	0 180	184	75	0 336
60	40	0 180	45	67	0 340
63	72	0 180	27	71	0 354
106	55	0 180	68	54	0 360
109	82	0 180	95	37	0 360
132	66	0 182	122	62	0 860
58	50	0 102	151	38	0 360
131	68	0 192	186	77	0 360
125	15	0 198	182	80	0 372
183	67	0 204	76	50	0 396
195	50	0 204	28	55	0 408
83	60	0 216	159	60	0 408
82	42	0 222	73	37	0 420
162	73	0 240	164	63	0 420
105	70	0 242	70	40	0 432
176	82	0 252	139	71	0 438
190	95	0 256	163	64	0 444
130	65	0 228	31	67	0 456
64	50	0 264	97	25	0 444
71	82	0 264	51	47	0 480
101	65	0 264	166	38	0 516
68	30	0 264	54	37	0 540
180	62	0 264	105	60	0 546
30	55	0 276	178	68	0 552

TABLE 23—PHTHALGINS—(Continued)

Case Number	Per Cent Phthalein 2 Hrs	Blood Urea	Case Number	Per Cent Phthalein 2 Hrs	Blood Urea
32	63	0.270	121	T	0.600
10	70	0.276	71	22	0.624
35	65	0.280	181	70	0.636
50	77	0.288	156	50	0.672
78	67	0.288	1	15	0.694
87	42	0.288	156	26	0.720
123	87	0.288	144	20	0.936
152	T	0.285	4	20	1.008
11	95	0.294	144	13	1.560
193	70	0.300	108	T	3.260

They quote the work of Javal as establishing the fact that the urea content of body fluids, edema, pleural and ascitic, equals in amount the blood urea. They found the normal urea in spinal fluid between 0.01 per cent and 0.05 per cent.

Cullen and Ellis<sup>36</sup> (1915) have shown that when the blood and spinal fluid are drawn at about the same time the difference in the amount of urea in the two fluids is rarely greater than 2 mg per 100 c c.

We have made comparative urea determinations on the body fluids and blood of twenty-eight different patients. Of these nineteen were spinal and six were peritoneal fluids. Table 23 shows the results, and they will be seen to correspond closely with those obtained by Soper and Granat. In the main the blood urea equals the fluid urea. Cases 54, 55, 57, 187 and 191 show rather marked differences. The fluids and blood from Cases 54, 55 and 57 were taken within a few minutes of each other. The fluids from Cases 55 and 57 were from very thick-walled ovarian cysts. The fluids from Cases 187 and 191 were taken at different times from the blood.

#### CONCLUSIONS

1 In the normal fasting adult the blood urea varied from 0.108 to 0.252 gm per liter.

2 The majority of cases of acute nephritis show an increased urea.

3 In mild chronic nephritis there is a normal or slightly elevated amount of blood urea. Cases of advanced chronic nephritis have a distinct increase. The effect of an associated cardiac decompensation is to further elevate the blood urea.

36 Cullen and Ellis Jour Biol Chem, 1915, 22, 511

TABLE 24—BLOOD PRESSURES \*

Case No	Age	Blood Pressure	Blood Urea	Case No	Age	Blood Pressure	Blood Urea
110	51	68	0.708	122	43	112	0.350
37	36	80	0.168	122	43	112	0.450
106	28	88	0.180	135	35	112	0.242
112	23	88	2.316	150	58	112	0.648
106	28	90	0.156	163	50	112	0.444
59	34	92	0.156	17	46	115	0.246
115	8	92	0.596	89	25	115	0.180
87	43	94	0.384	99	34	115	0.312
182	60	96	0.372	23	35	116	0.590
97	53	98	0.336	47	24	116	0.192
123	45	100	0.288	92	27	117	0.326
122	43	100	0.408	34	48	118	0.450
164	29	100	0.420	119	28	118	0.144
33	17	100	0.824	180	53	118	0.228
38	23	100	0.168	185	40	118	0.312
58	22	100	0.192	146		118	0.276
89	21	102	0.168	173	46	118	0.500
70	28	102	0.120	31	60	119	0.456
107	45	102	0.336	32	20	119	0.270
175	25	102	0.336	24	40	120	0.150
193	45	103	0.300	29		120	0.336
168	50	104	0.132	21	41	120	0.222
36	44	104	0.660	72	20	120	0.264
142		105	0.288	95	27	120	0.360
137	25	106	0.156	97	53	120	0.444
54	34	108	0.540	101	55	120	0.264
62	39	108	0.156	145		120	0.336
169	40	108	0.336	158	56	120	0.276
19	38	110	0.384	162	24	120	0.240
35	23	110	0.280	170	32	120	0.120
69	21	110	0.108	178	39	120	0.552
70	28	110	0.432	195	20	120	0.204
73	34	110	0.420	197	23	120	0.120
121		110	0.600	198	41	120	0.276
133	14	110	0.255	200	32	120	0.216
151	37	110	0.360	201		120	0.204
122	43	110	0.300	40	21	122	0.156
11		112	0.288	41	21	122	0.120

\* Blood pressures are systolic

TABLE 24—BLOOD PRESSURES \*—(Continued)

Case No	Age	Blood Pressure	Blood Urea	Case No.	Age	Blood Pressure	Blood Urea
50	67	122	0 288	151	37	140	0 660
88	28	122	0 180	171	18	140	0 168
148		122	0 394	181	42	140	0 636
176		122	0 252	189	43	140	0 180
25	26	123	0 168	190	45	140	0 256
81	38	125	0 216	104		142	0 204
144	39	125	1 512	109	47	142	0 180
60	22	126	0 180	130	53	142	0 180
68	50	126	0 360	157	45	142	0 348
103		126	0 192	166	22	144	0 225
205	35	128	0 210	113	26	145	0 324
129	33	130	0 360	140	46	145	0 276
156	32	130	0 672	194		145	0 264
26	22	130	0 252	209	35	145	0 180
78	54	130	0 288	67	40	148	0 156
79	57	130	0 228	126	35	148	0 370
102	35	130	0 336	7	72	150	0 034
140	46	132	0 240	22	16	150	0 372
189	62	132	0 438	84	42	150	0 312
144	39	132	1 560	128	50	150	0 276
9	43	130	0 264	184	42	150	0 336
188	45	130	0 180	108	47	152	3 360
196	26	132	0 108	27	56	150	0 334
206	34	132	0 360	16	33	154	0 224
204	60	132	0 216	20	67	154	0 150
28	33	134	0 408	10	54	154	0 278
127	65	134	0 240	131	37	154	0 192
156	32	134	0 720	124	24	155	0 264
8	54	135	0 210	15	27	156	0 228
30	32	135	0 276	116	28	156	0 426
155	34	135	0 240	207	50	160	0 408
90	28	136	0 204	134	47	162	1 020
6	48	137	0 120	136	33	162	0 480
75	80	137	0 264	165	64	162	0 168
105	47	138	0 546	48	51	163	0 144
180	34	138	0 264	114	60	163	0 224
149	50	140	0 312	203	63	163	0 270
68	50	140	0 264	55	46	170	0 248

TABLE 24—BLOOD PRESSURES\*—(Continued)

Case No	Age	Blood Pressure	Blood Urea	Case No	Age	Blood Pressure	Blood Urea
141	54	170	0.420	96	46	190	0.396
160	31	170	0.501	153	54	190	0.261
199	42	172	0.180	191	58	201	0.396
47		178	0.242	85	60	208	0.324
14	57	180	0.150	143	60	220	0.180
44	56	180	0.168	18	55	220	0.276
132	46	180	0.182	56	65	240	0.414
105	47	180	0.212	208	60	240	0.360
152	62	185	0.285	161	56	242	0.336
174	67	186	0.264	22	54	242	0.300
1	75	190	0.691	3	50	250	0.096
4	78	190	1.008	5	26	250	0.240
46	55	190	0.288	76	29	250	0.296

4 A high value occurring with a transient mechanical obstruction of the urinary tract does not necessarily mean a bad prognosis

5 In polycystic kidneys, with a very large amount of blood urea, and low phthalein excretion, the outcome may not be immediately fatal

6 The majority of cases of lobar pneumonia have a raised value. A bad prognosis should be given in those cases which show considerable increase

7 Approximately one-half of the cases of syphilis show a distinct elevation

8 In exophthalmic goiter there is an increase, and in myxedema, a decrease in blood urea

9 In primary anemia, nephrolithiasis, pyelonephritis, pyonephrosis, septicemia, streptococcic meningitis, Rocky Mountain spotted fever, pulmonary tuberculosis, diabetic coma, intestinal obstruction, malignancy, and common duct obstruction, we find a definite increase in most of the cases

10 A slight elevation occurs in valvular heart lesions, myocarditis, secondary anemia, urticaria, fractured skull, cerebral hemorrhage, concussion, bone cyst, traumatic pleurisy, arteriosclerosis and chronic arthritis

11 No changes were found in psoriasis, pityriasis rosea, epilepsy, meningococcic meningitis, diabetes and functional neurosis

12 The urea content of body fluids, in the majority of cases, agrees with the blood urea

13 The blood pressure was taken in 178 cases. Reference to the results, as given in Table 24, will readily show that there is no relation between blood pressure and the amount of blood urea

14 The results of phthalein excretion in ninety-six cases agree with the observation of others, who find in most cases the percentage of phthalein excreted is diminished along with increase in blood urea (Table 23)

# THE EFFECT OF CONTINUOUS ELECTRIC LIGHT IN EXPERIMENTAL ARTHRITIS<sup>\*</sup>

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It has been observed that a patient suffering from rheumatic pains and joints is very often relieved by the application of incandescent light either locally by means of one, two, or three bulbs with a metal reflector, or by a more general application in the form of the electric light bath. Although much is written in the literature on light as a therapeutic agent, we have been unable to find any previous work done to bring out experimentally this particular phase of treatment.

The following is the report of a study of experimental arthritis in rabbits and its treatment by means of the incandescent electric light.

Preliminary standardizations were made to ascertain (1) The amount of light that could be used on a normal rabbit without causing distress, loss of weight, or an increase in temperature, (2) the dosage of an organism that would produce in all cases an arthritis in from five to seven days, and (3) the size of rabbit best suited for bringing out the factors selected for study.

The first three series of rabbits were treated in a cage having glass sides, metal door and top, lighted continuously by two or three electric globes of the Edison Mazda, 110 volt, 150 watt type. The electric globes were suspended within the cage, giving a temperature of 15 to 20 degrees centigrade above the outside atmosphere or an average of 35 C. The fourth and fifth series were treated in open wire cages allowing free circulation of air on all sides. In these series the temperature was but 4 to 6 degrees higher than that of the surrounding atmosphere. The organism used was the *Streptococcus haemolyticus*, isolated from the crypts of the tonsils after removal, following an attack of acute tonsillitis and polyarthritis, dosage, one-fifth of a forty-eight hour blood agar slant growth. The rabbits were about 1,000 gm in weight.

The factors selected for study were (a) Number and extent of the joint lesions, (b) weight, (c) temperature, (d) leukocyte count.

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<sup>\*</sup> From the Departments of Therapeutics and Experimental Medicine, College of Medicine, University of Illinois.

<sup>\*</sup> Read before the Medical Research Club of the University of Illinois June 9, 1915.

Six rabbits were injected intravenously with the living streptococci. Three were placed in the closed cage, as described, for treatment and the other three in an open wire cage as controls.

Among the treated animals two developed arthritis, one having a single mild involvement, the other three mild lesions, a total of four joints involved. The third rabbit showed no lesion. Of the untreated rabbits, all had arthritis, one had three slight lesions, the second three moderately severe and the third four, a total of ten.

A second similar series showed still better results. Two treated rabbits escaped arthritis and the remaining one had four moderately severe joints. Of the untreated rabbits, one had three severe joints, the second four severe and the third five severe lesions, a comparison of four in the treated to twelve in the untreated animals.

A third series of twelve rabbits gave results of four lesions in six treated animals against ten in six untreated rabbits.

In the next series, the first treated in open wire cages, the dose of living streptococci was slightly increased. Six treated rabbits gave ten joint lesions, three not having lesions. Six untreated had sixteen joint lesions, none of the animals escaping.

In a further series of eight rabbits, four treated gave five lesions and four untreated nine joint lesions. This time the rabbits were not treated until arthritis developed, and then the light treatment was pushed. The treated rabbits improved, while the others continued to have new involvements.

The most reliable factor for study was the actual formation of pathological lesions in and around joints, with impairment of function, pain, swelling or exudation and confirmation of our clinical findings by necropsy.

The joint lesions were classified as mild, moderate or severe. An arthritis was considered as mild when impairment of function and tenderness on palpation were transitory in character and swelling was either absent or of a mild degree, moderate, when impairment of function and tenderness were of longer duration and the enlargement had largely disappeared at necropsy, and severe, when the swelling was readily noticeable, the function entirely lost, and either marked exudation or suppuration present at autopsy in the joint and periarticular tissues.

TABLE SHOWING COMPARISON OF THE TOTAL RESULTS IN TWENTY-TWO TREATED AND TWENTY-TWO UNTREATED RABBITS

	Treated	Untreated
No. of joints involved per rabbit	1.2	2.58
Severe lesions	2.0	11.0
Average gain in weight in grams	65.0	38.25
Average daily temperature	103.3	103.8
Average maximum temperature	104.9	105.5



As will be seen in Table 1, the number of joints involved per rabbit in the twenty-two treated was 12 or a total of twenty-seven, two of these being classed as severe. In comparison we find that the untreated animals developed fifty-seven arthritic lesions, or 2.58 per rabbit, over twice as many per animal as in the former group. In further confirmation of this, the untreated animals had eleven severe lesions or five times as many as the treated animals.

In a previous paper<sup>1</sup> by one of the contributors on the prophylactic treatment of experimental arthritis with vaccines, it was observed that the weight curve of the treated animals was more uniform than the weight curve of the untreated. This led to the observation of

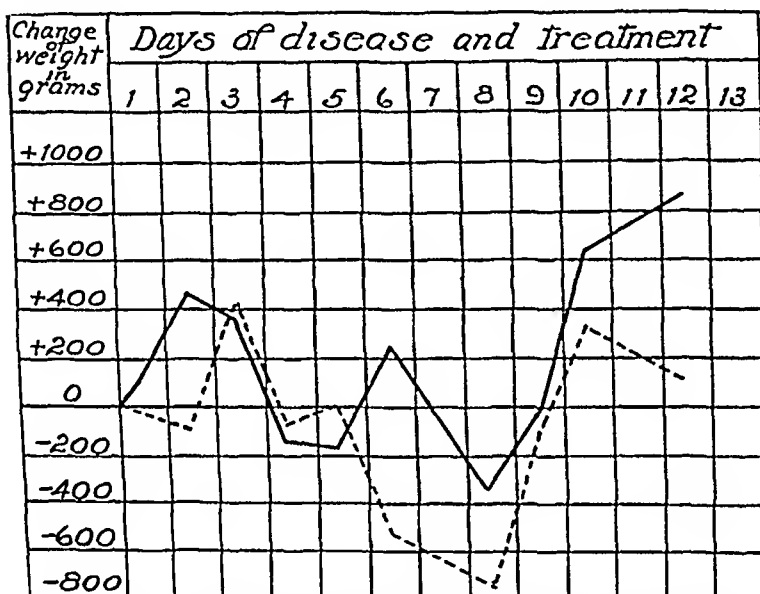


Chart 1—Composite weight curve of twenty-two treated and twenty-two untreated rabbits. Solid line, treated animals, broken line, untreated animals.

the weight changes in this series of experiments. Somewhat similar results were noted. The rabbits under the rays of the incandescent light gained on an average almost twice as many grams per animal as those untreated, or an average of 65 to 38 gm. All the animals did not gain in weight. There were individual losses in each group but the total gain favored the treated animals, as shown in Table 1.

To eliminate as many variable factors as possible, the total average gain was based on the weight of the animals at the time of death from the streptococcus infection, or when they were chloroformed for necropsy. The latter period was from two to six weeks after the injection. However, the animals were weighed at regular intervals during the course of the experiments and Chart 1 illustrates much

<sup>1</sup> Moore, J. J. Jour Infect Dis, 1914, xv, 215

better than words the marked variations in the average composite weight curve of the two groups. It will be observed that up to the fifth day the variations are approximately the same, the difference shown being in favor of the untreated animals. After that date, which corresponds with the appearance of arthritic lesions, although the curves are somewhat parallel, there is a great difference in degree. Of the animals living on twelfth day the total composite weight gain for the treated was 837 gm and for the untreated 142 gm.

Again, the composite temperature curve of the treated animals is not as high as that of the other group, as is illustrated by Chart 2. This is important, as the atmospheric temperature in the cages with the light was usually from 15 to 20 degrees Centigrade higher than in the cages of the controls. Another point of interest is that the

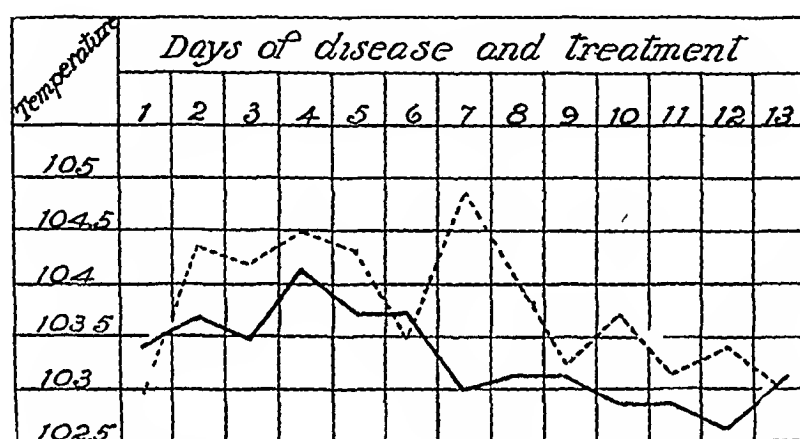


Chart 2—Composite temperature curve of twenty-two treated and twenty-two untreated rabbits. Solid line, treated animals, broken line, untreated animals.

average maximum temperature of the treated animals was 0.5 degree Fahrenheit lower than the controls, as shown by Table 1. The same variation was found in the average daily temperature of the two groups. The leukocyte count of the two series showed but little variation. The last two series eliminated the heat factor to a considerable extent, the temperature in these experiments being only 4-6 degrees C above the surrounding temperature.

#### CONCLUSIONS

The production of experimental arthritis in rabbits was either prevented, or was much milder in degree, in animals treated with the continuous incandescent electric light than in the controls not treated.

Rabbits treated with the incandescent electric light after developing acute experimental arthritis recovered more rapidly than the control animals.

# THE INTRASPINAL TREATMENT OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM, ACCORDING TO THE METHOD OF SWIFT AND ELLIS<sup>†</sup>

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CLEVELAND

In 1912 Swift and Ellis<sup>1</sup> described a method for the intraspinal treatment of syphilis of the cerebrospinal axis. They felt that since practically all drugs were excreted into the subarachnoid space either poorly or not at all, a direct application of salvarsan to the meninges would have a distinctly greater curative effect than when salvarsan was given only by the intravenous route. That intraspinal injections of salvarsan or neosalvarsan, dissolved in salt solution, were far too irritating to be practical was shown by their<sup>2</sup> experiments on monkeys. The medium which Swift and Ellis<sup>1, 3</sup> finally decided on was the blood serum of a patient, withdrawn shortly after the intravenous administration of salvarsan. This blood serum, diluted with salt solution, was introduced into the subarachnoid space, without severe symptoms of meningeal irritation and with beneficial results in syphilis. This method has been criticized on the ground that it was unnecessary because the intravenous injection of salvarsan was all-sufficient in its action. In the light of the recent investigations of Adler,<sup>4</sup> Hall,<sup>5</sup> Swift,<sup>6</sup> Camp<sup>7</sup> and others, who have shown that no arsenic, or only the merest trace of it, appears in the spinal fluid after the intravenous administration of salvarsan, it would seem that the direct method is the only way in which arsenic can be introduced into the subarachnoid space in adequate dosage.

Another criticism has been that a therapeutically negligible amount of arsenic was introduced in the "autosalvarsanized" serum. Draper<sup>8</sup> has shown that no more than 0.25 milligram to 0.5 milligram of salvarsan can be introduced repeatedly with safety into the subarachnoid space. Swift<sup>6</sup> and Adler<sup>4</sup> have shown that blood serum, removed a

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1 Swift, H F, and Ellis, A W M. New York Med Jour, July 13, 1912

2 Ellis, A W M, and Swift, Homer F. Jour Exper Med, 1913, xviii, 4

3 Swift, Homer F, and Ellis, A W M. THE ARCHIVES INT MED, 1913, xii, 331

4 Adler, Herman M. Boston Med and Surg Jour, 1914, clxxi, 900

5 Hall, G W. Jour Am Med Assn, April 24, 1915, lxiv, 1384

6 Swift, H F. Jour Am Med Assn, 1915, lxv, 209

7 Camp. Lancet-Clinic, 1915, cxiii, 116

8 Draper, George. THE ARCHIVES INT MED, 1915, xv, 16

short time after the intravenous administration of salvarsan, contains amounts varying between these limits, and seldom below them

It would seem, then, that by the intraspinal injection of auto-salvarsanized serum we have a method of introducing arsenic in non-toxic doses into the subarachnoid space. Several other methods for the introduction of neosalvarsan and salvarsan into the subarachnoid space have been described, notably that of Ravaut<sup>9</sup> and Wile's<sup>10</sup> modification of this method and that of Ogilvie<sup>11</sup>. A discussion of these methods would be out of place in this paper as we have had no personal experience with them.

Since the communications of Swift and Ellis, numerous reports regarding the efficiency of autosalvarsanized serum in the treatment of syphilis of the central nervous system have appeared. A brief review of them is of considerable interest.

McCaskey<sup>12</sup> gave twenty intraspinal injections to seven patients. His longest observation extended over a period of three months. He states that some of his patients improved very much under treatment. He gives no data as to the effect of the treatment on the laboratory findings. In another article<sup>13</sup> the same author describes some technical modifications of the method, but fails to state whether or not his results were favorable.

Hough<sup>14</sup> treated six paretics. As two of his cases received but one treatment each, his report is based on his results in four cases. Three showed some symptomatic improvement, while all four showed marked improvement in the blood and spinal fluid findings.

Cutting and Mack<sup>15</sup> report their results in six cases of paresis and one case of cerebral syphilis. The mental condition in all but one showed no improvement. There was no marked change in the neurological findings. The cell counts in the spinal fluids showed a constant and marked reduction, although the Wassermann reaction remained positive and there was no effect on the globulin content.

In eight cases of paresis treated by Myerson<sup>16</sup> definite changes were seen in the spinal fluid findings after treatment. No real clinical improvement was seen.

Pillsbury<sup>17</sup> used the intraspinal treatment in eleven cases of advanced paresis. Six of these patients showed improvement either

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9 Ravaut, P. *Bull et mém Soc méd d hôp de Paris*, 1913, xxxvi, 752

10 Wile, U. J. *Jour Am Med Assn*, 1914, lxii, 1163, *ibid*, 1914, lxiii, 173

11 Ogilvie, H. S. *Jour Am Med Assn*, Nov 28, 1914, lxiii, 1936

12 McCaskey, G. W. *Jour Am Med Assn*, 1914, lxii, 187

13 McCaskey, G. W. *Jour Am Med Assn*, 1914, lxii, 1709

14 Hough, W. H. *Jour Am Med Assn*, 1914, lxii, 183

15 Cutting and Mack. *Jour Am Med Assn*, 1914, lxii, 903

16 Myerson. *Boston Med and Surg Jour*, May 7, 1914

17 Pillsbury, L. B. *Jour Am Med Assn*, 1914, lxiii, 15

in the clinical condition or in the laboratory findings. There was only one case which showed decided clinical improvement.

Mapother and Beaton<sup>18</sup> report their results in four cases of early paresis. They gave five combined intravenous and intraspinal treatments to each patient. There were no appreciable changes noted in the mental condition of the patients. No changes in the blood and spinal fluid Wassermann reactions, which were performed quantitatively, were seen. The pleocytosis and increased globulin content remained unaffected in all cases.

Riggs and Hammes<sup>19</sup> gave 100 intraspinal treatments to twenty-four patients. In each patient who received over four combined injections the blood Wassermann reaction became negative, except in one case of juvenile paresis. The blood and spinal fluid findings became normal in every way in 75 per cent of the cases of tabes thus treated. These changes were accompanied by marked clinical improvement. In paresis the results of treatment were less encouraging. The clinical improvement was rarely marked even after a great deal of treatment had been given.

Litterer<sup>20</sup> reports a series of four cases of paresis and eleven cases of tabes or cerebrospinal syphilis in which the intraspinal injections were used. Ten of the paretics showed improvement. All the cases of cerebrospinal syphilis and of tabes showed marked betterment. Four had had a great deal of salvarsan or neosalvarsan intravenously with no more than temporary improvement of their symptoms.

McClure<sup>21</sup> treated four cases of cerebrospinal syphilis, two of tabes dorsalis, one of taboparesis and two of paresis, a total of nine cases. None of his cases were observed for a longer period than five months. All the cases of tabes and cerebrospinal syphilis showed definite improvement, both clinical and in the laboratory findings. One case of paresis showed no improvement, while the other improved greatly.

Krida<sup>22</sup> has given seventy-two intraspinal injections in eighteen cases. Out of eight cases of tabes there were four which showed improvement and four which failed to improve. In four cases of paresis there was no improvement in the mental symptoms. One paretic died after an intraspinal injection.

Ayer<sup>23</sup> has reported his results in sixteen cases. His report is of great value on account of the length of time over which he was able

18 Mapother, E., and Beaton, T. *Lancet*, London, 1914, clxxxvi, 1103.

19 Riggs and Hammes. *Jour Am Med Assn*, 1914, lxi, 1277.

20 Litterer, W. *Lancet-Clinic*, 1915, cxiii, 359.

21 McClure, C. W. *Boston Med and Surg Jour*, 1914, clxvi, 520.

22 Krida. *Albany Med Ann*, 1914, xxxv, 243.

23 Ayer, James B. *Boston Med and Surg Jour*, 1914, clxx, 452.

to observe his patients. The shortest observation is for a period of thirteen months. His most flattering results were in cerebrospinal syphilis, in which condition Ayer believes that persistent treatment in favorable instances, will accomplish a cure. In tabes he believes that an arrest of the process is often to be expected. His results in paresis were far less satisfactory.

Draper,<sup>8</sup> continuing the observations on Swift and Ellis' original series, reports his results in a series of twenty-five cases. The report is exceptionally careful and detailed. The series includes conditions ranging from tabes associated with painful crises up to brain involvements with marked mental disturbance. There was marked clinical improvement in all classes. The pain and ataxia were usually greatly relieved. Those with bulbar involvement or with mental disturbance showed much improvement, not only in the symptoms, but in the laboratory evidences of the disease. He found that there was apparently no limit to the number of intraspinal injections which might be given when the autosalvarsanized serum was used.

Smith<sup>24</sup> gave fifty-three injections to twelve patients. In some of his cases, however, he injected undiluted blood serum into the subarachnoid space. In this point only did his technic differ from the original Swift-Ellis method. He used Wile's modification of the Ravaut method fourteen times in twelve additional cases. With this latter method he had unfortunate results, and concludes that it is too dangerous to use. His results with the Swift-Ellis technic were excellent. Clinically, he found marked improvement, and the serological findings in the spinal fluid either diminished or returned to normal. The pleocytosis in the spinal fluid was affected first, next the Wassermann reaction was diminished, but the increased globulin content was the slowest of the three tests to disappear.

The general conclusion which can be drawn from the above reports indicates that by this method some changes may occur in paresis, but that much permanent improvement is scarcely to be expected. On the other hand, the effect of the treatment in cerebrospinal syphilis and tabes dorsalis seems to be extremely beneficial. The symptomatic improvement is often marked and a diminution or a complete disappearance of the serological findings in both the blood and the spinal fluid may be expected in most instances.

The method has been criticized on the ground that it is dangerous. A careful search of the literature shows the following fatalities.

Lorenz<sup>25</sup> treated five patients with paresis. Two died. He then gave up this particular technic, stating that it "has in our hands been

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24 Smith, L. D. Jour. Am. Med. Assn., 1915, lxiv, 1563

25 Lorenz. Wisconsin Med. Jour., 1913, xii, 171

very irritating and caused alarming symptoms" Pillsbury<sup>17</sup> reports the death of a paretic shortly after an intradural treatment Krida<sup>22</sup> also reported the death of a paretic Neither Swift and Ellis,<sup>1, 3</sup> Ayer,<sup>23</sup> Diaper,<sup>8</sup> nor Smith<sup>21</sup> have had a fatality in their extensive series It is noteworthy that the reported deaths have been among paretics, and that no fatalities have occurred after the treatment of tabetics The number of fatalities in the total number of treatments is not alarming, considering the desperate outlook in this condition No account is taken of fatalities occurring after any kind of intradural treatment except that of Swift and Ellis

We wish to report our results with the intraspinal injection of autosalvarsanized serum in syphilitic affections of the central nervous system The number of our cases is limited but the value of our report may be increased by the length of time that some of them have been under observation Our first patient came under treatment in January, 1913, and the second one a short time later (March, 1913) These two patients were under our care so short a time that they are scarcely worthy of consideration

In addition to these two preliminary cases we have observed one case of extremely acute cerebrospinal syphilis, eight cases of definite tabes or cerebrospinal syphilis and one case of paresis

We have followed rigidly the Swift-Ellis technic From one-half hour to one hour after an intravenous injection of salvarsan or neosalvarsan from 40 to 50 c c of blood are withdrawn with aseptic precautions from the patient by venipuncture, using a McRae needle fitted to a 50 c c centrifuge tube The tube is then corked with a sterile cork, and after the blood has clotted, the clot is separated from the sides of the tube with a sterile platinum wire The serum is then separated in a rapid centrifuge, then withdrawn with a sterile capillary pipet and ejected into a sterile, graduated, glass-stoppered mixing cylinder Especial care must be taken to have the serum absolutely free from red blood cells and fibrin Sufficient sterile normal sodium chlorid solution is added to make the desired dilution, the cylinder is stoppered and is placed in a water bath at 56 C for one-half hour On the following day lumbar puncture is performed Fifteen c c of spinal fluid are allowed to run out into a graduated test tube, when the barrel of a 25 c c Luer syringe is attached to the free end of the lumbar puncture needle by the intervention of a section of rubber tubing 12 inches long, fitted with slip-joint connections When the spinal fluid appears in the syringe (which is held upright so that it may be used as a graduated funnel) the serum mixture is poured in it This is allowed to flow by gravity

ABSTRACT OF CASE HISTORIES

An abstract of the histories of these cases follows

CASE 1—(Table 1) W. I S Cerebrospinal syphilis Male, 29 years old Married. The intraspinal treatment was begun March 13, 1913 The year before the patient consulted us he had been temporarily unable to void urine and had had to be catheterized Five months later he began to have shooting pains in the legs which were thought to be sciatica Attacks of pain in the

TABLE 1—(CASE 1.) CEREBROSPINAL SYPHILIS

W. I S, aged 29. Cerebrospinal syphilis Duration. one year Syphilis admitted Result marked improvement

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm.	Serum Intra- spinously cc pct.	
		Cells per c mm	Noguchi Globulin Test	Wasser- mann Reaction No cc			
2/ 7/13	+++	153	++	01, ++ 02, +++			..
2/13/13					914, 03		.
2/26/13					914, 05		
3/13/13					914, 06		
3/14/13 *	—	16	+	03, +++		20	40
5/14/13	.				914, 06		
5/15/13			..	03, +++		25	40
6/22/13 †			..	.. .	914, 06		
7/ 8/13		0	—	03, ++	606, 06	25	40
7/10/13				04, +++			
8/21/13		.	.		606, 05	25	40
8/22/13				02, +			
				03, +++			
10/ 3/13	..				606, 055	.	.
10/16/13		.			606, 055	.	.
12/ 1/13 ‡					606, 05		
12/ 3/13	—	33	—	05, — 10, +++		22	40
1/26/14					606, 05		
1/27/14		13	—	05, — 10, +++		25	40
2/ 8/14	+++	. ....	.			.	
3/26/14					606, 05		
3/27/14	.	3	±	08, +++		25	50

\*Patient has been having HgCl<sub>2</sub> injections

† General condition poor Luetic orchitis

‡ General condition much improved

legs and abdomen were a frequent occurrence Diplopia and ptosis of the left eyelid appeared three weeks before he was seen by us At examination the pupils reacted sluggishly to both light and accommodation and were unequal in outline The knee and ankle jerks were absent The sensations of touch, pain, heat and cold were diminished all over the body except on the face and neck The blood showed a very strongly positive Wassermann reaction The spinal



fluid showed a great globulin increase, 153 cells to the cmm, and a Wassermann reaction strongly positive with 0.2 cc of the fluid. The process was advancing rapidly, for between the time of the first examination and the first treatment, a period of nineteen days, he grew rapidly worse. It was almost impossible for him to get about on account of an ever increasing paresis of the right leg.

The improvement was very slow in this case. His general condition was poor and he had a complicating luetic orchitis. It was not until he had received eight intravenous injections and four intraspinal injections, stretching over eight months, that he reported himself as being free from pain in the legs, and suffered only an occasional twinge in the chest. His improvement has been steady since that time. His last treatment was in March, 1914.

*Summary of Treatment*—This patient has been under observation over two years. In that time he has received twelve intravenous injections of salvarsan (a total of 5.4 gm) and seven intraspinal injections. Further, he has received much mercury, both by injection and by inunction.

*Results and Present Condition*—In May, 1915, the patient reported that he had had only one attack of pain in the last year. He has returned to his business, which he is pursuing as usual. He has regained the power in his right leg and he walks perfectly well. The physical findings are much the same as when he was first observed, except that the sensations have returned to a marked degree. There has been marked improvement in the laboratory findings in both the blood and spinal fluid.

**CASE 2**—(Table 2) W M B. Moderately advanced tabes. Male, 45 years old. Single. The intraspinal treatment was begun May 8, 1913. The patient was infected with syphilis at the age of 25. He walked unsteadily and had attacks of lancinating pains in the legs for two years previous to the time at which he was first seen by us. He had had three intravenous injections of salvarsan (0.6 gm each) before consulting us. At examination, the pupils were unequal but reacted to light and accommodation. The knee and ankle jerks were absent. There was a large area of hypalgesia over the outside of the left thigh. Romberg's sign was present. The Wassermann reaction in the blood was strongly positive. The spinal fluid showed a moderately increased globulin content, 75 cells per cmm, and a Wassermann positive in 0.1 cc of spinal fluid.

After seven injections of neosalvarsan and five intraspinal injections the laboratory findings showed decided improvement. The globulin disappeared and the cell count was reduced from 75 to 5 per cmm. Sensory changes were less marked and the patient walked better. It is interesting to note that the lancinating pains in this case disappeared after the first intraspinal treatment and have never returned. The patient was then put on mercurial inunctions, and after a short time he became very uncertain on his feet and had much increased numbness and tingling, so much so that he could not walk without assistance. The mercury was discontinued and he received four intravenous injections of salvarsan and one intraspinal injection with a very marked improvement in his ability to walk.

After receiving eighteen intravenous injections and fourteen intraspinal injections, the patient was so much improved that he went west and took up his duties as a ranch owner, performing all the duties of ranch life, walking, driving, riding, plowing and so forth, without difficulty.

He returned, after an absence of ten months, when we found his blood Wassermann reaction negative. The globulin content of the spinal fluid was not increased. The cells were within normal limits and the Wassermann reaction was strongly positive only when 0.5 cc of fluid was used.

*Summary of Treatment*—This patient was under observation over two years. He has received in all twenty intravenous injections of salvarsan or neosalvarsan (the equivalent of 10.7 gm salvarsan) and fifteen intraspinal injections. He had practically no reaction after either form of treatment.

TABLE 2—(CASE 2) TABES DORSALIS

W M B, aged 45 Moderately advanced tabes dorsalis Duration two years Syphilis admitted Result marked improvement

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum		
		Cells per c mm	Noguchi Globulin Test	Wasser- mann Reaction No c c		Intra- spinously c c	pct	
5/ 2/13	+++	75		01, +++				
5/ 7/13					914, 06			
5/18/13					914, 06	25	40	
5/19/13								
6/ 3/13					914, 06			
6/ 4/13			20	+	01, +++	914, 06	25	40
6/18/13						914, 06		
6/19/13			10	+	01, +++		25	40
7/ 1/13						914, 09		
7/ 2/13			5	—		914, 09	25	40
7/16/13	Pupils equal Used Hg +++				914, 09			
7/17/13				02, +++		25	40	
7/31/13					914, 09			
8/ 6/13								
8/27/13								
9/12/13					02, +			
					03, +++			
9/15/13						606, 05		
9/29/13						606, 05		
10/13/13						606, 05		
11/ 1/13	+++				606, 05			
11/ 6/13								
11/ 7/13					606, 05			
11/17/13								
12/ 1/13 *								
12/ 2/13								
1/ 8/14								
1/ 9/14								
2/ 5/14								
2/ 6/14								
2/19/14	Numbness	10	—	01, +++		25	40	
2/20/14								
3/ 5/14								
3/ 6/14								
3/19/14								
3/20/14								
4/ 6/14								
4/ 7/14 †								
2/ 6/15 ‡								
2/15/15								
2/16/15		1	—	05, +++	914, 09	25	50	
3/ 2/15					914, 09			
3/ 3/15		0	—			25	50	

\* Surer on feet Walks better

† No sensory disturbance subjective or objective Can walk and run

‡ Also negative when done with two and three times the usual amount of patient's serum

*Results and Present Condition*—The patient is now able to follow his usual occupation without difficulty April 30, 1915, he wrote that he walked normally, though he felt a little stiffness from his knees down and that he could cover three or four miles a day without difficulty There has been no change in the physical findings except that practically no sensory disturbances exist There has been a marked improvement in the serological findings From a functional and symptomatic point of view this patient is vastly improved

CASE 3—(Table 3) H O B Male, aged 34 Single Cerebrospinal syphilis with very acute onset of symptoms Had been drinking heavily and was brought to the Cleveland City Hospital for what was presumed to be

TABLE 3—(CASE 3) CEREBROSPINAL SYPHILIS

H O B, aged 34 Acute cerebrospinal syphilis Result marked improvement, Cleveland City Hospital

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc pct	
		Cells per cmm	Noguchi Globulin Test	Wasser- mann Reaction No cc			
3/21/14 *	+++	550	++	01, +++	0.45	.	
4/13/14 †		155	Faint +	01, +++			
4/27/14				02, +++			
4/28/14	+++					25	40
5/2/14							
5/12/14					0.6		
5/19/14					0.6		
5/20/14		30	+	02, +++		25	40
6/2/14	+++				0.6		
6/3/14		30	+	03, +++		25	40
6/5/14							
6/18/14					0.6		
6/19/14		15	+			25	40
7/8/14					0.6		
7/9/14		10	+	03, +++		25	50
7/27/14	-				0.6		
7/28/14 ‡		5	0	03, +++		25	50
8/9/14 §		7	0	02, +++			
5/31/15 ¶		3	0	05, + 01, +++			

\* Wild delirium followed by unconsciousness with fever and signs of acute meningeal involvement Double papillitis

† Mercury binitodid,  $\frac{1}{2}$  gr intramuscularly, eighteen doses

‡ Serum followed by very severe reaction Heavy trace of albumin in urine

§ Discharged from the hospital with slight facial paresis and paresis of left arm Much improved

¶ Only slight slurring of speech and paresis of left arm No treatment from 8/9/14 to 5/21/15

delirium tremens Two weeks after admission the patient developed a paresis of the left arm and of the left side of the face associated with a marked rigidity of the neck and double Kernig's sign and a double Babinski reflex The pupils reacted to light The right was larger than the left The temperature rose to 103.6 and the pulse to 108 He had incontinence of both urine

and feces The spinal fluid was turbid, showed 550 cells per cmm, a heavy Noguchi globulin reaction and a positive Wassermann reaction in 0.1 cc of the spinal fluid Under intramuscular injections of mercury binioid, gr ½, of which he received eighteen, together with large doses of potassium iodid, the acute symptoms cleared up, but the patient was very weak His mentality was slow and his speech halting His first intraspinal injection was given April 28, 1914 During three months following the patient received seven intravenous injections of salvarsan, a total of 4.05 gm, and four intraspinal injections of 25 cc of 40 per cent serum and two intraspinal injections of 25 cc of 50 per

TABLE 4—(CASE 4) TABES DORSALIS

C H Z, aged 44 Tabes dorsalis several years' duration Syphilis denied. Result marked improvement

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc pct	
		Cells per cmm	Noguchi Globulin Test	Wasser- mann Reaction No cc			
6/ 4/14					914, 06		
6/ 5/14		62	++	02, +++		25	40
6/18/14					914, 09		
6/19/14		15	+	04, +++		30	40
7/29/14					914, 09		
8/ 1/14		0	±	05, —		30	40
				10, +++			
9/ 9/14					914, 09		
9/10/14		6	—	05, —		20	40
				10, +++			
10/ 1/14					914, 09		
10/ 2/14				08, +++		20	40
10/30/14*					606, 04		
10/31/14				08, ++		30	40
				10, +++			
12/ 2/14					606, 04		
12/ 3/14		1	—	07, +++		30	40
1/28/15					606, 05		
1/29/15†		0	±	05, —		15	40
				10, +++			
3/18/15					606, 05		
3/19/15		0	—	10, ±		25	40

\* Gained in weight No crises since 10/2

† No crises Occasional twinge in leg

cent serum After the last injection the patient had a severe reaction, characterized by pains in the head and abdomen and by albuminuria While under intraspinal treatment the patient gained 20 pounds in weight His mentality improved greatly and his general strength increased He left the hospital and returned to his work as a manager of a shoe store, which he carried out to the satisfaction of his employers He was seen again nine months after his discharge from the hospital The patient was well nourished His speech was slightly halting, but questions were answered intelligently He showed no tendency to the speech defects typical of paresis The pupils reacted a little sluggishly to light The paresis of the left arm was still present but no other abnormalities were made out on physical examination The blood Wassermann

reaction was negative. The spinal fluid showed three cells per cubic millimeter, a negative Noguchi globulin reaction and the Wassermann reaction gave a strongly positive reaction with 0.7 cc of the fluid.

In this case the acuteness of the symptoms at onset is very striking. Under treatment the symptomatic improvement was very marked, while the serological findings in blood and spinal fluid remained almost the same, except for the diminution in cells and globulin content in the spinal fluid.

*Results and Present Condition*—Observation after nine months without treatment showed that the patient had returned to economic efficiency and it is interesting to note that during this time his serological improvement had become very marked. His process has not only been arrested but has receded to an apparently harmless degree of latency. He should, of course, receive treatment until all the serological signs of the disease have disappeared.

*Summary of Treatment*—This patient received seven intravenous injections (a total of 4.05 gm salvarsan) and six intraspinal injections preceded by 9 gr of mercury biniodid intramuscularly, during a period of a little less than five months.

CASE 4—(Table 4) C II Z Tabes dorsalis (moderately advanced) Man, 44 years old. Had been troubled for some years with gastric crises and with incontinence of urine. No history of a luetic infection could be obtained. The pupils were pin point and did not react to light. Knee and ankle jerks were lacking, muscle sense was impaired and Romberg's sign was present. Received first intraspinal treatment June 5, 1914. After the first combined treatment there was a marked subsidence of pain, and after the third treatment he began to show decided improvement in general condition. The spinal fluid taken after two combined treatments showed a disappearance of the lymphocytosis and with 0.5 cc the Wassermann reaction was negative.

*Summary of Treatment*—He has received neosalvarsan or salvarsan intravenously nine times (the total being equivalent to 4.6 gm of salvarsan) and nine serum injections. The reaction to the intraspinal treatments were at first severe but latterly they have been less marked.

*Present Condition*—Clinically his present condition is greatly improved. The pains have disappeared, except for recrudescences in mild form when he is fatigued. His weight has increased, he feels well and his economic efficiency has been restored. Physical examination shows no change in pupils or reflexes but the Romberg sign is less marked and the muscle sense is improved. The laboratory findings are very gratifying. The cell count is normal, globulin is absent, and even when 1.0 cc of spinal fluid was employed the result of the Wassermann reaction was negative ( $\pm$ ).

CASE 5—(Table 6) Mrs W A D Early tabes. Female, 34 years of age. Married. Complained of occasional incontinence of urine and stumbling. The symptoms had been in evidence for one and one-half years. Infection had taken place twelve or thirteen years previously. At that time she had received "pills" for a year only. Examination showed inequality of pupils with failure to react to light, absence of knee and ankle jerks and Romberg's sign. For a year before consulting us some soluble mercurial preparation had been administered intensively. Under this therapy she made some improvement, but it was slight and very slow. The Wassermann reaction, using blood serum, was strongly positive and the spinal fluid showed 95 cells per cmm a positive globulin test, a Wassermann reaction when only 0.1 cc was employed.

The improvement in this case after the institution of intravenous and intraspinal treatment was rapid and striking. After the first two treatments she reported that she was able to run up stairs from the basement to the second story, while previously in ascending stairs she had to stop after climbing

up a few steps "to take the twist out of her legs" The subarachnoid fluid showed the Wassermann reaction to be less than one-fifth as strong as it had been. Altogether this patient has been under observation six months

*Summary of Treatment*—The patient has taken six injections of neo-salvarsan or salvarsan (the total being equivalent to 30 gm of salvarsan) and has been given two intraspinal injections

*Present Condition*—When the spinal fluid was examined last the lymphocytosis and the trace of globulin had disappeared, and the Wassermann reaction was negative with 0.5 cc, though positive with 10 cc In addition, the clinical result in this case has been very striking The incontinence has cleared up, the gait has improved She is much stronger and can accomplish more The pupillary reaction and the ankle and knee jerks are unchanged

TABLE 5—(CASE 5) TABES DORSALIS

Mrs W. A. D., aged 34 Early tabes dorsalis Syphilis admitted Result marked improvement

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc    pct	
		Cells per c mm	Noguchi Globulin Test	Wassermann Reaction No    cc			
10/14/14	+++	95	+	01, +++	914, 06	25	40
10/19/14					914, 09		
10/20/14					914, 09		
11/13/14*					05, +		
12/30/14					01, +++		
12/31/14†	±—	1	—	05, — 10, +++	914, 09	21	50
1/22/15					606, 04		
2/ 5/15					606, 04		
3/ 5/15							
4/ 8/15							

\* Already feels much better

† Coordination much improved

‡ Also negative when reaction was performed using two and three times usual amount of patient's serum

CASE 6—(Table 6) D W H Moderately advanced tabes Man, aged 39 He acquired syphilis in 1901 His treatment was interrupted after six months on account of very severe typhoid fever which intervened Following convalescence from typhoid, iodid and mercury were taken by mouth periodically, and since then he has had broken courses of mercury The first symptoms of nervous disturbance came in March, 1913 After this he had a nervous breakdown associated with dyspepsia In October, 1914, he noted stiffness and numbness in the extremities Soon after he had severe pain in the back and had much difficulty with locomotion on account of "stiffness in his legs"

The patient has received a portion of his treatment from Dr H M Brundage of Columbus, who has very courteously furnished us with a synopsis of his findings When the patient was first seen by him Dec 28, 1914, the blood serum Wassermann reaction was negative and the spinal fluid showed 150 cells

per cubic millimeter, a decided trace of globulin and a strongly positive Wassermann reaction, the quantities varying from 0.1 to 0.5 cc (expressed in terms of modified technic) Dr Brundage administered a total of three intravenous and three intraspinal injections. The patient noted decided improvement three days after his first treatment.

When we saw the patient the pupils showed inequality but reacted promptly to light and accommodation. The knee jerks and ankle jerks were absent. Muscle sense was impaired. There were marked sensory changes. A slight Romberg sign was present and the patient had a typical tabetic gait. The spinal fluid showed that the cell count had diminished to 2 per cubic centimeter, the butyric acid reaction was only faintly positive and the Wassermann reaction was negative with 0.5 cc, but strongly positive with 1.0 cc.

TABLE 6—(CASE 6) MODERATELY ADVANCED TABES

D W H, aged 39 Moderately advanced tabes Result marked improvement

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc pct	
		Cells per c mm	Noguchi Globulin Test	Wassermann Reaction No cc		cc	pct
Previous to March, 1915 <sup>†</sup>	—	150	+++	0.2, +++	†	‡	
3/13/15	—						
4/9/15					0.4	30	40
4/10/15		2	Faint +	0.5, — 1.0, +++			
5/7/15					0.4		
5/8/15		0	—	0.5, — 1.0, +++		30	50
6/11/15					0.4		
6/12/15				0.7, — 0.9, + 1.0, +++		28	50
7/30/15					0.5		
7/31/15	—	1	Faint +	0.5, — 1.0, ±		32	50

\* While he was under the care of Dr W H Brundage of Columbus, Ohio, to whom we are indebted for the above data.

† Three injections of 0.6 gm followed by three intraspinal treatments of 20 cc of 50 per cent serum-NaCl mixture.

‡ Marked clinical improvement.

*Summary of Treatment*—He has received in all seven intravenous injections of salvarsan, a total of 3.5 gm, and seven intraspinal injections of salvarsanized serum.

*Present Condition*—At present the appreciation of pain has returned in both legs, muscle sense is accurate and the vibratory sense has returned over the greater part of both legs. The patient has no pains and no stiffness, he takes exercise and goes about his business with zest and is living a normally efficient existence. The Wassermann reaction is negative in the blood. The globulin content of the spinal fluid is not increased. There is one cell to the cubic millimeter and the Wassermann reaction on the spinal fluid is but a plus-minus reaction when 1.0 cc of the spinal fluid is used. This case can fairly be considered at present a clinical and serological cure.

CASE 7—(Table 7) H R Moderately advanced tabes Male, aged 32 Married. First intraspinal treatment given April 23, 1914 Patient was infected eleven years ago There were no noticeable secondary manifestations so that no treatment was taken until two years after the infection, when sores appeared in the mouth and throat For five years the patient had suffered excruciating, lancinating pains in the legs The crises of pain sometimes lasted for thirty-six hours There was occasionally involuntary micturition The patient was a well developed young man The pupils were widely dilated and reacted to light The knee and ankle jerks were absent There was a slight Romberg's

TABLE 7—(CASE 7) MODERATELY ADVANCED TABES

H R, aged 32 Moderately advanced tabes Duration five years Syphilis admitted Result improvement

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously c c pct	
		Cells per c mm	Noguchi Globulin Test	Wasser- mann Reaction No c c			
3/28/14	+++	...	.	.	914, 09	25	40†
4/22/14		...		.			
4/23/14		10	++	04, — 05, +++	.		
5/27/14		...		.	606, 04‡	25	40
5/28/14	.	0	.	05, — 10, +++	.		
6/17/14		...		.	606, 04	25	40
6/18/14		3	+	05, — 10, +++	.		
7/22/14		.....		.	606, 045§	20	40
7/23/14		.....		05, — 10, +++	.		
9/ 3/14		...		.	606, 04	20	50¶
9/ 5/14	+++	0	+	05, — 10, +++	.		
1/ 6/15		..	..	10, —	914, 06	25	40
1/ 7/15	.	..					

\* This reaction was so strong that it was given with one-eighth the usual amount of the patient's serum

† Very severe reaction

‡ Leg pains worse

§ Feels wonderfully well, little pain

¶ Pains have returned Not so severe

sign The blood showed a strongly positive Wassermann reaction The spinal fluid showed a marked increase in the globulin content, 10 cells to the cubic millimeter, and a Wassermann reaction positive with 05 c c of the fluid

*Summary of Treatment*—This patient was under our observation for ten months, during which time he received six intravenous injections of salvarsan or neosalvarsan (a total equivalent to 265 gm of salvarsan) and six intraspinal injections In addition to this he received intramuscular injections of mercury salicylate with regularity

*Results and Present Condition*—Symptomatically the patient showed improvement in that the lightning pains abated temporarily Later they became trouble-



some again. The spinal fluid findings are interesting in that after five intraspinal injections they disappeared entirely, although the blood still remained positive. His last combined treatment was in January, 1915. In April, 1915, he wrote us the following: "I have the pains some, but less severe. My head is clear. I go sometimes a week without a sign of a pain. . . sleep well, which certainly goes to show that either one of the treatments" [intraspinal or mercurial] "or the combination of the two has not been without result." In July, 1915, seven months after his last treatment, we are informed that the patient died of an acute nephritis following a severe, widespread mercury poisoning.

CASE 8—(Table 8) L. B. D. Advanced tabes. Male, aged 40. Married. First intraspinal treatment Nov. 11, 1914. Infected with syphilis twelve years previously. There were no secondary manifestations, so that nothing but local treatment was ever given. The spinal cord symptoms had been present for a

TABLE 8—(CASE 8) ADVANCED TABES

L. B. D., aged 40. Advanced tabes dorsalis. Symptoms of several years' duration. Syphilis admitted. Result: slight improvement.

Date	Blood Wassermann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc pet	
		Cells per cmm	Noguchi Globulin Test	Wassermann Reaction in cc Sp. Fluid			
8/26/14	+++	23	++	0.3, +++	914, 0.6	20	40
11/10/14							
11/11/14							
12/ 1/14		2	+	0.2, +++	914, 0.8	25	40
12/ 2/14							
12/18/14		1	+	0.3, ++ 0.4, +++	914, 0.9	25	50*
12/19/14							
1/ 4/15		13	++	0.2, + 0.3, +++	606, 0.4	22	50
1/ 7/15							

\* Walks better

number of years. He had lost much weight. His color was yellowish. He was distinctly emaciated and anemic. The pupils were unequal in size and did not react to light. The knee and ankle jerks were exaggerated. There was a marked ataxia. The blood showed a strongly positive Wassermann reaction. The spinal fluid showed a marked increase in globulin, 23 cells per cubic millimeter, and a Wassermann reaction which was positive when 0.3 cc of the fluid was used. We were inclined to expect little, if any, improvement in this case in the light of the low cell count combined with the symptoms of rapid degeneration.

*Summary of Treatment*—He received four intravenous injections of salvarsan or neosalvarsan (a total equivalent of 1.92 gm of salvarsan) in a period of two months. This was preceded by two months of intensive mercurial injections.

*Results and Present Condition*—The present condition is unchanged. The cell count in the spinal fluid fell from 23 to 13 per cubic millimeter, while the globulin content and the Wassermann reaction showed no diminution.

CASE 9—(Table 9) A J K Moderately advanced tabes Male, aged 31 We had seen this patient in consultation in November, 1911 At that time he gave a history of having been infected six years previously and of "taking pills" for three years, almost constantly He then had a sensation of a band around the waist and numbness in the hands and feet Even at that time signs of moderately advanced tabes were definite and unmistakable The blood Wassermann reaction was strongly positive On account of the then prevalent distrust of salvarsan in neurological conditions, vigorous mercurial treatment was employed exclusively With this he grew rapidly worse and had a partial paraplegia When seen again in January, 1914, he had been having daily mercury injections for six months and a dose of neosalvarsan intramuscularly He was up and about and felt fairly well The blood Wassermann reaction was

TABLE 9—(CASE 9) MODERATELY ADVANCED TABES

A J K, aged 31 Moderately advanced tabes dorsalis Duration over three years Syphilis admitted Result slight improvement

Date	Wasser- Blood mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc pct	
		Cells per cmm	Noguchi Globulin Test	Wasser- mann Reaction in cc Sp Fluid			
11/25/11	+++						
1/17/14	+						
11/28/14	+*						
12/ 3/14		125	+++	02, +++	914, 09	25	40
12/ 4/14			+++	02, +++	914, 09	21	50
12/29/14			+++	02, +++	606, 05	25	50
2/ 5/15		13	+++	02, + 03, +++	606, 04	30	40
2/ 6/15		0	++	02, — 03, +++	606, 04	30	50
3/19/15							
3/20/15		0	++	02, — 03, +++	606, 04	30	50
5/29/15							
5/30/15		0	Not examined	02, + 03, +++			

\* Reaction +++ when twice usual amount of patient's serum was used

very faintly positive We began the Swift-Ellis treatment in December, 1914 Then the pupils were small and showed no light reaction, the knee and ankle responses were abolished and there was a slight Romberg sign Mentally the patient seemed rather slow The spinal fluid findings were cell count, 125, globulin, very heavy trace, Wassermann reaction, strongly positive with 02 cc The Lange colloidal gold test was positive

*Summary of Treatment*—This patient has been under our immediate supervision for only six months He has had five intravenous injections, two of neosalvarsan and three of salvarsan (the total being equivalent to 25 gm of salvarsan), and four serum injections

*Present Condition*—We feel that he has been under observation too short a time to permit drawing any conclusions of especial value The spinal fluid lymphocytosis disappeared rapidly, and the patient reports that he feels stronger

and better and that he is able to do more work on his farm this summer than he could a year ago. The history, with the long duration of the condition, the severity of the symptoms, and the extent of involvement, pointed in advance to the need for prolonged treatment.

CASE 10—(Table 10) J L S. General paresis. Male, aged 45. Married. Infected with syphilis twenty years ago. Has taken small amounts of mercury at intervals. Two years ago the patient began to have stomach trouble. He was seen in March, 1915. His speech was thick and he had the classical symptoms of an early paresis. The pupils were irregular and unequal in size. The knee and ankle jerks were exaggerated. There were no definite sensory changes. The blood showed a strongly positive Wassermann reaction. The spinal fluid showed a cell count of 25, a very marked globulin increase and a Wassermann reaction positive in 0.2 cc of spinal fluid. The patient had lost much weight.

TABLE 10—(CASE 10) EARLY PARESIS

J L S, aged 45. Married. Early paresis. Result improvement especially in serological findings.

Date	Blood Wasser- mann Reaction	Cerebrospinal Fluid			Intra- venous Salvarsan gm	Serum Intra- spinously cc    per cent	
		Cells per c mm	Noguchi Globulin Test	Wasser- mann Reaction No    cc			
3/20/15	+++	25	++	0.2, +++	0.35 * 0.4 0.4 0.45	20	40†
4/23/15							
5/21/15							
6/10/15							
6/25/15							
6/26/15		0	++	0.3, — 0.4, +++	0.5	28	50‡
7/12/15				0.5, —			
7/13/15				1.0, +++			

\* Between 3/20 and 4/23 intensive mercury treatment. No improvement.

† Lange colloidal gold test typical parietic curve.

‡ Lange much less marked.

and was running down rapidly. Between April, 1915, and July, 1915, he has received five intravenous injections of salvarsan (a total of 2.1 gm) and two intraspinal treatments, one of 40 per cent and one of 50 per cent serum. After the first three intravenous injections the patient showed very little change in his condition. In fact, his difficulty in speaking and writing became worse. The spinal fluid withdrawn after the three intravenous injections showed very little improvement. Immediately after the first intraspinal treatment the patient was mentally much worse. He slurred in his speech pitifully and was almost incapable of looking after himself. This condition cleared up and about two weeks later the speech was distinctly clearer. The patient concentrated better. A spinal fluid examined at this time (July 13, 1915) showed no cells, a positive globulin, a Wassermann reaction negative in 0.5 cc of spinal fluid, but positive in 1.0 cc.

While this patient has been under observation too short a time to warrant any conclusions being drawn from the case the changes in the spinal fluid two weeks after the first intraspinal treatment are of considerable interest.

We have given fifty-nine intraspinal injections of autosalvarsanized serum in ten cases. Further, we have given fourteen similar treatments not included in the above series, making a total of seventy-three injections. Following these injections we have seen no symptoms, temporary or permanent, which could in any way be attributed to injury to the central nervous system. We have seen no deaths, paralysis or bladder disturbances. One of our patients died of an intercurrent condition seven months after the cessation of treatment. Two of the patients have experienced no discomfort from the procedure. When gastric crises or lancinating pains exist, we have learned to expect attacks of pain, in all ways similar to the pre-existing crises. These crises usually follow the treatment after an interval of from two to four hours and they are often very severe. Their duration is usually short, and they are followed by much increased periods of freedom from pain. As the treatment continues these postoperative attacks become less and the spontaneous crises often disappear entirely.

It is of interest to note that those patients who have had these reactions of pain following the treatment have showed greater and more rapid improvement than those who had no discomfort from the procedure.

We have found that the increased globulin content in the spinal fluid is very resistant to treatment. A moderate increase in globulin often persists after several treatments, as in Cases 8 and 9, where only a very slight decrease in globulin has occurred after three treatments. The pleocytosis disappears rapidly. In Case 1 lymphocytosis of 550 per cubic millimeter came within normal limits after six intravenous and four intraspinal injections. Cell counts of 150 or below usually diminish to normal limits after from one to three treatments. We have found that the Wassermann reaction in the spinal fluid is the most obdurate of the laboratory findings. The reaction often persists in the larger doses of spinal fluid, long after the other laboratory findings have come within the normal limits.

The changes in the physical findings which we have noted under the intraspinal treatment have been a partial or complete disappearance of disturbances of sensation, lessening or disappearance of ataxia and a marked increase in weight and strength. In no case, so far observed, have we seen absent deep reflexes return, nor have we seen any change in the pupillary reactions.

The abatement or disappearance of symptoms has been most striking. In every instance in which lancinating pains were present, they have either disappeared completely or have diminished so much that they have ceased to be a real annoyance. In Case 3, gastric crises which had nearly incapacitated the patient, have disappeared. Very

striking is the rapid improvement in the general condition, in weight, in strength and in return of the ability to carry on the daily routine of employment, in other words, the practical ending of invalidism. In some cases this improvement in the general condition can be attributed to the abolition of pain, but in others (notably Cases 3, 5 and 9) in which pain had not been a feature, this general betterment was noted. Vesical incontinence in one case has been so much less frequent that it has almost ceased to be an annoyance.

#### RESULTS

The results in six of these ten cases has been a symptomatic improvement so emphatic that the patient's economic efficiency has been restored. They are able to work and to enjoy life to all intents and purposes as normal individuals.

We feel that the best results will be obtained in cerebrospinal lues, and in tabes of the early or moderately advanced types. In far advanced tabes the results are in most cases dubious to say the least. Our own experience with paresis is so limited that we should have no right to make any generalization. It seems probable to us, however, that very little can be done to improve permanently a paresis once it is well established.

In concluding we feel that we can state fairly that the Swift-Ellis method is safe when the original technic is followed out to the letter. The claim of the originators that it is a valuable adjunct to the treatment of syphilitic involvement of the central nervous system is sustained as far as tabes dorsalis and cerebrospinal syphilis are concerned. It is a method which is not essential in all cases, but which applied carefully and controlled intelligently will bring about definite amelioration in symptoms and in laboratory signs where other accepted modes of attack have failed.

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# PROTHROMBIN AND ANTITHROMBIN FACTORS IN THE COAGULATION OF BLOOD <sup>†</sup>

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Few have studied the prothrombin and antithrombin factors of coagulation of the blood in human cases. Howell<sup>1</sup> devised methods to study these factors and has reported a deficiency of prothrombin in hemophilia with relative excess of antithrombin, a diminution of antithrombin in cases of spontaneous thrombosis and no abnormality in the cases of purpura he studied.

Whipple<sup>2</sup> reported increased amounts of antithrombin and a prothrombin deficiency in hemorrhagic cases, but his results are to be criticized in that he did not take into consideration normal variations, and that dog blood was used to control human. Austin and Pepper<sup>3</sup> have made studies on the coagulation of oxalated plasma. In one case of purpura they found delayed coagulation on recalcification in the presence of thromboplastic solutions and attributed it to increased antithrombin. Since our work was begun, Hess,<sup>4</sup> using Howell's methods, has published the results of a study of these factors in scurvy, which were negative.

Whipple and Moss<sup>5</sup> have pointed out that a knowledge of how these factors may vary in hemorrhagic disease is important in considering treatment, for on theoretical grounds one would not treat a case of bleeding due to an increased amount of antithrombin the same as one due to a deficiency of prothrombin.

In certain cases perhaps one might be able to predict when thrombosis was apt to take place by a fall in the amount of antithrombin and be able to give something to prevent thrombus formation.

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1 Howell THE ARCHIVES INT MED, 1914, xiii, 76

2 Whipple THE ARCHIVES INT MED, 1913, xi, 637

3 Austin and Pepper THE ARCHIVES INT MED, 1913, xi, 305

4 Hess AM JOUR DIS CHILD, 1914, viii, 386

5 Whipple and Moss Forchheimer's Therapeutics of Internal Diseases, 1914, v 801 D Appleton & Co

With Dr Howell's and Dr Thayer's stimulating interest and help a further study of the blood in various diseases, with reference especially to the content in antithrombin and prothrombin, has been made, with the hope that we could say definitely that there are bleeding cases due to increased amounts of antithrombin and others due to diminished amounts of prothrombin, and that diminished amounts of antithrombin occur only in cases that are subject to or have thrombosis. A consideration of these tests, the normal variations of the factors, and the findings in various pathologic conditions form the basis of this paper.

#### METHOD OF OBTAINING BLOOD

Specimens of blood were drawn by venepuncture into an all-glass graduated syringe, previously sterilized and rinsed with normal salt solution, from which a measured amount was put into a tube with a measured amount of 1 per cent sodium oxalate in 0.9 per cent salt solution. Usually 5 cc of blood were mixed with 0.7 cc of the oxalate solution. However, the series of plasmas tested at any one time were diluted the same.

Precaution was taken that the venepuncture was done cleanly, so that the needle was not scraped about in the tissue, thus covering it with the tissue juice (thromboplastic material). Care was taken to get no air bubbles in the syringe as the blood was drawn, though in some instances where this occurred, no very definite differences in the prothrombin or antithrombin were noted. If any hemolysis had taken place in the plasma, as from traces of water left in the syringe or other cause, it was rendered valueless for prothrombin and antithrombin determinations because of liberated thromboplastic material.

Each specimen being mixed with the oxalate solution was brought to the laboratory and centrifuged at high speed, about 3,000 revolutions a minute, for just twenty minutes. The plasma was then pipetted off from the cellular elements and examined for prothrombin and antithrombin.

#### PROTHROMBIN

(A) *Method of Testing*—To test the relative amount or efficiency of prothrombin, the method of recalcifying the oxalated plasma as described by Howell,<sup>1</sup> was used. The method employed is as follows.

Five drops of the plasma were placed in five tubes (1.3 cm diameter, 6.8 cm high with flat bottom) and to these were added in series 1, 2, 3, 4, and 5 drops of a calcium chloride solution. The time, called the prothrombin time, that it took the first clot to form which was not dislodged on inversion of the tube, was taken to represent the prothrombin, that is, the clotting time with the optimum amount

of calcium It was rare not to find at least two tubes clotting in practically the same time, not infrequently four of the five tubes would clot within a minute of each other If the minimum was long, twelve to fourteen minutes, then it was more usual to see a well-marked graded difference in the clotting (i e., for example, the 5-drop tube clotted in 24 minutes, the 4-drop in 18, the 3 in 14, and the 2 in 12 minutes) than if six to eight minutes was the minimum time Perhaps this was because a proportional difference was less easily detected in the shorter period of time

After the calcium chlorid was added, the tubes were immediately shaken to mix it with the plasma Care was taken that the tubes were not jarred when the clotting was going on, they were, however, gently tilted, equally in the different specimens, to see if clotting had taken place The test was always made within two hours after the collection of the blood and usually within an hour Allowing the plasma to stand some hours before the test is made will usually not only vary the prothrombin time, but often the amount of calcium necessary to obtain it Very slight changes may occur in the prothrombin time of a plasma which has stood two or three hours The test was made at room temperature, which though not taken, we believe was always about 70 F

It has been shown by Lee and Vincent,<sup>6</sup> among others, that a plasma in which the platelets are kept as nearly as possible intact by using greased cannulas and drawing the blood directly into oxalate, will vary the platelet content of the plasma and in turn vary the prothrombin time, being longer the fewer the platelets We found in three instances, that a difference of centrifuging fifteen or thirty-five minutes plasma collected by our methods made no appreciable difference in the prothrombin time, or in the amount of calcium needed for this time

Two calcium chlorid solutions were used during our study, one made from fused calcium chlorid, the other of pure recrystallized calcium chlorid, containing water of crystallization The latter when compared with the former usually caused a given plasma to clot in the same time, though sometimes it caused a clot to form a half minute sooner

It is advisable to use for this test a solution of the calcium chlorid containing water of crystallization, for numerous solutions were made from different stocks and those made from deliquescent calcium chlorid always acted the same Those from fused calcium chlorid often caused a delay, even as much as four minutes in the prothrombin

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6 Lee and Vincent THE ARCHIVES INT MED, 1914, xiii, 398



time, and the difference between the clotting times of a plasma with different amounts of calcium was distinctly greater than when the solutions of deliquescent calcium chlorid were used. This is perhaps because the fused calcium chlorid contained something that interfered with clotting.

The optimum amount of calcium was always essentially the same unless the contrary is stated, provided the dilution of the blood with oxalate solution was the same. Though the amount of oxalate used to dilute a given blood may vary, the prothrombin time is the same within a minute.

(B) *Normal Prothrombin*—Ninety-one determinations of prothrombin time, which varied from six to fourteen minutes, averaging nine and one-half, were made from sixty-six normal persons between April, 1914, and March, 1915. In comparing two prothrombin times, the longer time was taken to represent a less amount of prothrombin or a relative deficiency of prothrombin, the shorter the reverse.

During the time these normals were tested, seventy-three cases with various diagnoses were studied whose prothrombin time (eighty-nine determinations) was found to be between six and fourteen minutes. The accompanying table (Table 1) shows the frequency of the varying normal prothrombin times.

TABLE 1—SHOWING NORMAL VARIATIONS OF PROTHROMBIN TIME

Prothrombin time*	Minutes				
	6	8	10	12	14
Determinations on normal persons	14	27	27	19	4
Determinations on diseased persons	17	28	25	12	8

\* Clots only recorded on even minutes

During warm weather the prothrombin time was usually shorter than in cold weather. Studies now being made tend to show that the temperature at which the test is made, and at which the plasma is kept before the test is made, will vary the prothrombin time, so that for accuracy the test should be run at the same temperature, preferably 21 C.

There was a distinct tendency for the cases of a given day to be grouped in a high, medium or low range, that is, one would see on a different day variations of 10 to 14, 6 to 8 or 10, or 8 to 12, that is, not over 4 minutes difference. However, there are three instances among the diseased and but one instance among the normals in which 6 and 14 occurred at the same time.

One cannot say from the cases studied by the methods used that either six minutes or fourteen minutes is abnormal for prothrombin time, though the observer on different occasions may have the impression that six or fourteen in certain instances is abnormal.

What effect diet, exercise, time of day, acidity of the blood, etc., may have on this reaction has not yet been determined

A delayed prothrombin time, spoken of as a low prothrombin, may be dependent on the antithrombin content of the plasma. One must realize that this test for prothrombin is a relative test of efficiency, because in an oxalated plasma we have not only prothrombin but antithrombin, fibrinogen and thromboplastin. If there is a high antithrombin content, the clotting on recalcification would perhaps be somewhat delayed provided the prothrombin were not increased. It might, with the same high antithrombin content, be still more delayed if the prothrombin were diminished, but if the antithrombin were normal or less than normal and there was a delayed prothrombin time, one could say the prothrombin was the lacking element. Addis<sup>7</sup> has suggested that the delayed prothrombin time occurring in hemophilia is not due to a diminished amount of prothrombin but to an alteration that makes it slowly available for use. This may be true of any delayed prothrombin time, there being no way to determine the actual amount of prothrombin. The amount of fibrinogen in human cases is probably always enough to give a clot within the normal time, though its firmness may be changed.

A certain amount of thromboplastin is normally present in plasma in the form of disintegrated blood plates, etc. A marked lessening of this element could probably cause a delayed prothrombin time.

#### ANTITHROMBIN

(A) *Method of Testing*—The antithrombin was tested for in the same specimen of blood as the prothrombin, usually two to three, sometimes as many as six hours after the blood was drawn.

A method for testing antithrombin with which we have had as yet little experience has recently been described by Hess,<sup>8</sup> in which antithrombin from the cases to be tested is added to an oxalated plasma and the times of clotting on recalcification with the optimum amount of calcium, compared. Whipple, among others, tested for antithrombin by the amount of thromboplastic material required to neutralize the antithrombin.

The test we used is of the type described by Howell.<sup>1</sup> All the plasmas in which antithrombin was to be determined were slowly heated simultaneously on a water bath to 60 C., thus destroying the prothrombin and precipitating the fibrinogen. These were filtered, the filtrate containing only antithrombin as far as elements of coagulation are concerned.

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7 Addis Jour Path and Bact, 1911, xv, 427

8 Hess Jour Exper Med, 1915, xxi, 338

For each antithrombin test a series of tubes was set up with one drop of antithrombin in each tube, to which was added a varying number of drops of thrombin, usually 2, 3, 4 and 5 drops, and then these two substances were allowed to remain in contact for a given period of time, usually fifteen minutes. It is important that the tubes be twisted so that few drops of thrombin and antithrombin get well mixed and this should be done at once after the two substances are in the tubes so that the clots to be compared have the thrombin and antithrombin in contact an equal length of time. After the given interval had elapsed the same amount of a fibrinogen solution (usually 10 drops) was added to each tube. The tubes were then shaken to mix the materials and frequently looked at to see when the first clot appeared. Those tubes containing the least antithrombin would clot first, and those with the greatest, last.

Thrombin was prepared according to Howell's<sup>9</sup> method and kept in watch crystals. To obtain a solution of thrombin it was only necessary to dissolve the contents of a watch crystal in distilled water, the amount varying with the strength of the thrombin. Later observations showed that thrombin made by carrying the process through only to the stage of dialysis, though not entirely purified from other protein substances, was free from other elements of coagulation and yielded a satisfactory and stronger solution. It should be used unfiltered, as filtering weakens it.

For fibrinogen, dried oxalated cat's plasma made according to Howell's method was usually used. This was kept in watch crystals, redissolved in normal salt solution and filtered.

(B) *Consideration of an End Point*—Difficulty was found in obtaining a fibrinogen plasma which would give a good firm clot with thrombin in about three minutes, and which would give a similar clot in the presence of antithrombin in a period of time of over ten minutes, an amount of time found necessary to distinguish differences readily. Dried plasmas would not act always in the same manner. Some of the difference seemed to be due to the individual animal.

A given antithrombin, thrombin and fibrinogen mixture that clots if undisturbed in ten minutes as a solid jelly (i. e., with a period of but a minute when it is in a half jellied condition) if shaken frequently, causes a lumpy or perhaps sliding jelly-like clot to form in very closely the same time, which, if then left undisturbed, will become a solid jelly in perhaps fourteen to twenty minutes or even longer. If the same combination is shaken more violently, often flocculi will appear in

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<sup>9</sup> Howell. Am Jour Physiol, 1910, xxvi, 453, *ibid*, 1913, xxvii, 264

about the same time as the solid jelly did in the first instance, but to reach the solid jelly stage will then usually take much longer

Several series of antithrombin determinations were made on the same specimens with different fibrinogen solutions. Some gave flocculi, others a firm jelly and some a sliding jelly or lumpy clot. The comparisons between the different specimens were very similar, provided one read for the end-point the time when a clot of any sort first appeared. A solid clot made a neater and more easily distinguishable end-point. Flocculi were easier to read than sliding jelly or lumpy clots. If a shriveled-up, veil-like clot occurred it was impossible to tell when it first appeared.

Using the same solutions, slight differences in the amount of antithrombin may cause differences in the type of initial clot.

If flocculi are to be read as an end-point, the tubes must be examined and shaken frequently to break up these small white particles easily adhering to the glass. On the contrary, to obtain a solid jelly end-point, the tubes must be disturbed as little as possible. All tubes between which comparisons are to be drawn must be tilted or shaken equally.

(C) *Choice of Fibrinogen Solution*—Difficulty in getting a series of tubes to clot as solid jellies led to attempting the use of different fibrinogen solutions.

A dried, clear cat's plasma was made by a method suggested by Dr. Howell, similar to the previous one he described, but dialyzing the plasma against 0.7 per cent NaCl with 0.05 per cent  $\text{KH}_2\text{PO}_4$  for one hour, changing the solution at the end of half an hour, instead of a twelve-hour dialysis against 0.9 per cent salt solution. This method usually yielded a better fibrinogen solution than the older method, but still was often unsatisfactory. Weaker fibrinogen plasma was obtained from dogs.

Fluorid, magnesium sulphate and undialyzed oxalated plasmas dried and redissolved were unsatisfactory.

Solutions of pure fibrinogen prepared according to a modification of Hammarsten's method [precipitation of an oxalated plasma with saturated NaCl solution, centrifuging the precipitate and then washing with half saturated NaCl solution and redissolving in 2 per cent NaCl (adding a few drops of 1 per cent solution of sodium bicarbonate to aid solution, if necessary) and repeated once or twice] gave the best material because it allowed a solid jelly clot to form in the presence of strong antithrombin in a period of time permitting one to distinguish a real difference between two specimens. The difficulty with such a solution is that it cannot be kept for use for much more than six days.

One precipitation with the saturated sodium chlorid yielded a fibrinogen solution suitable for this test. Alkali weakens the effectiveness of the fibrinogen.

(D) *The Desirable Time to Have Clots Form*—Thrombin and fibrinogen react quantitatively, as is shown by the curve in the chart (taken from an average of several tests). This chart shows the effect of antithrombin on clotting when previously allowed to stand for a definite period in contact with thrombin. The less thrombin there is in proportion to the antithrombin the greater the time for the clot to form.

Besides changing the amount of thrombin to lengthen or shorten the time the clot appears, one can do so by lengthening or shortening

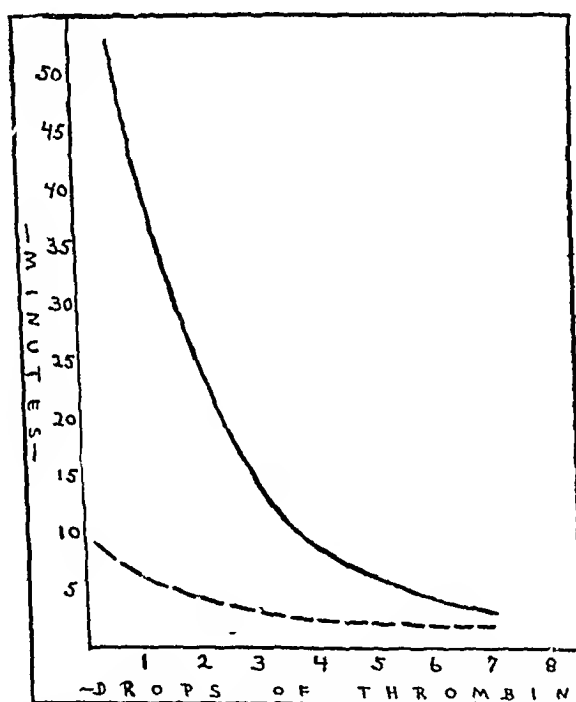


Chart showing that thrombin and fibrinogen react quantitatively. Solid line = thrombin + antithrombin + fibrinogen. Broken line = thrombin + fibrinogen.

the interval that the thrombin and antithrombin remain in contact. This may also change the type of clot.

The materials were always used in such amounts as to cause the first clot to appear in between eight to twenty minutes. If clotting took place rapidly it was difficult to distinguish differences between specimens, if too slowly the end point was difficult to determine.

(E) *Use of Antithrombin Factor in Comparison of Cases*—To compare the antithrombin of a series of specimens determined at the same time with the same solutions, time alone is sufficient, but to com-

pare antithrombin from different cases determined at different times with different solutions, the time in which the clot appears is unsatisfactory

None of the materials used are stable, temperature varies their action, all lose power on standing. Individual watch crystals of thrombin and fibrinogen plasma made from the same stock vary slightly, the difference depending very likely on the speed with which they were dried.

Heating plasma to 60 C, if done rapidly or slowly, will change somewhat the amount of antithrombin. The amount will also vary if the plasma is heated to 59 or 61 C.

If specimens are collected within about an hour of each other, heated simultaneously and tested at the same time with the same amounts of solutions, their antithrombin content will bear a fairly constant relationship to each other, often varying a little. The relationship if 1 to 1 might become as much as 0.86 to 1 or 1 to 1.15 when repeated tests are made. Such variation is probably due to technic, size of drops, the amount of mixing of thrombin and antithrombin, etc.

The relationships of two specimens will be maintained for at least six hours. Specimens of antithrombin kept on the ice for eighteen hours showed usually the same relationship to each other as when first tested. Though it was evident from the clotting time that antithrombin on standing loses power.

In view of the fact that the relation between a series of specimens keeps constant for hours, and time seems an unsatisfactory way to express antithrombin, the following scheme was devised to allow cases tested at different times to be compared.

A normal control was run with all the cases studied, often two controls, sometimes more. The added time of the specimens from the case clotting between eight and twenty-five minutes was divided by the similar figure for the control and this factor used to express the amount of antithrombin, and was designated as the antithrombin factor. The factor for a single comparison between tubes containing the same amount of thrombin determined at the same time, is known as a single series factor. At least three satisfactory series, not infrequently six, were run to obtain the antithrombin factor. An example of how these factors are obtained is given in Table 2.

To each specimen 1 drop of antithrombin was added to the varying drops of thrombin noted and allowed to remain in contact during the interval given and then 10 drops of fibrinogen were added.

If any one series gave a factor varying widely from the other series this was discarded, provided at least three other series remained which clotted in the suitable time, and the average of these was taken.

for the antithrombin factor This factor would, as a rule, fall close to the single series factor of the clots which clotted between ten and eighteen minutes

For antithrombin determinations, specimens of blood must be diluted equally with oxalate solution, because the amount of the antithrombin will vary with dilution A difference of from 5 to 4 c c of blood with 0.7 c c of oxalate will vary the factor from 1 to 0.87 ±

In the collection of specimens sometimes there may have been differences of 0.75 c c of blood

TABLE 2—SHOWING METHOD OF OBTAINING THE ANTITHROMBIN FACTOR

Drops of Thrombin	Time Before Fibrinogen Added minutes	Clotting Time minutes	Clotting Time Control minutes	Single Series Factor
1	15	40 *	40 *	?
2	15	24	19	1.26 †
3	15	12 +	10	1.2 + †
4	15	9	7	1.28
5	15	6	5½	1.09
3	20	15	12	1.25 †
4	20	12	9½	1.26 †

\* No clot in

Second column shows interval thrombin and antithrombin remained in contact before fibrinogen was added

Third column shows time clots formed in presence of antithrombin of case

Fourth column shows time clots formed in presence of antithrombin of control

The average of the series factors of those series that clotted in a desirable time (the marked † figures) is the antithrombin factor, which is 1.25

(F) *Normal Antithrombin*—The variation of antithrombin in normal human beings as determined by the method described above varies as is shown in Table 3 A study of from six to four normals on nine different occasions representing forty-eight observations on thirty-eight individuals was made These normals were second year medical students, medical graduates, and laboratory attendants from 22 to 38 years of age, except that those tested on November 9 were four surgical patients recovering from hernia operations and fractures

To obtain the degree of variation in the antithrombin factor the added time of a series of tests for the case with the highest antithrombin was divided by the lowest, and vice-versa By excluding the case with the lowest antithrombin in each series the antithrombin factors will show less wide variations In some series there was one case that had distinctly less antithrombin than the others No one case had

distinctly more than the others. In using normals as controls the chances of variation in the antithrombin factor would tend to be plus rather than minus, provided the cases ranged in the vicinity of most of the normals.

If the cases of November 18 are excluded, because they were tested with an unsatisfactory fibrinogen solution, the greatest variation of the antithrombin factors in the other eight series is 1.34-0.73 +, and after excluding the case with the least antithrombin from each series the greatest variation is 1.21-0.82.

TABLE 3—NORMAL VARIATIONS OF ANTITHROMBIN

Date	No. of Cases	No. of Series of Determinations	Widest Variation in Single Series *	Variations Excluding Least Antithrombin †	Average Antithrombin Factor ‡	Factor Excluding Least Antithrombin §
July 22	5	5	1.30-0.77	1.15-0.86	1.15-0.86	1.15-0.86
Oct 30	6	6	1.30-0.77	1.25-0.80	1.25-0.80	1.21-0.82
Nov 7	6	5	1.35-0.73	1.11-0.89	1.25-0.80	1.11-0.89
Nov 9	4	4	1.33-0.75	1.10-0.90	1.28-0.78	1.05-0.94
Nov 11	6	7	1.38-0.72	1.26-0.78	1.3 -0.76	1.21-0.82
Nov 18 ¶	6	7	1.6 -0.62	1.5 -0.66	1.46-0.68	1.3 -0.74
Dec 9	4	4	1.4 -0.68	1.33-0.75	1.34-0.73	1.21-0.82
Jan 6	6	5	1.25-0.80	1.25-0.80	1.20-0.82	1.16-0.85
Jan 7	5	4	1.30-0.77	1.25-0.80	1.28-0.78	1.21-0.82
Average	5	5	1.35-0.73	1.24-0.81	1.28-0.77	1.17-0.84

\* The widest variation in any single series of tests obtained by dividing the longest time of clotting of thrombin and fibrinogen in the presence of antithrombin by the shortest and the shortest by the longest. Figures in other columns obtained in similar way.

† Widest variation in any single series after excluding case with the least antithrombin.

‡ Average antithrombin factor of all series and cases.

§ Average factor if case with least antithrombin is excluded.

¶ Tests of November 18 were run with an unsatisfactory fibrinogen solution, which probably explains why they show the widest variation.

It is felt that one can take for the widest extremes of factors from normals 1.34-0.73 + and for the usual variation 1.21-0.82.

In order to figure the antithrombin factor for a case, it is evident that it would vary considerably if we used a low or a high control. To be absolutely sure that we are dealing with pathological figures we must obtain an antithrombin factor below 0.55 or above 1.81. To be beyond the usual variation of normal, when we may be reasonably sure we are dealing with pathological conditions, we should obtain a factor below 0.68 and above 1.47.

The normals with low antithrombin should have been repeated to see if they were persistently low or fluctuated with diet, time of day, etc., but unfortunately this was not done. Some normals repeated on different days showed a rather constant relation to each other.



## RELATION OF PROTHROMBIN TO ANTITHROMBIN

The prothrombin as well as the antithrombin was determined in this series of normals. One might expect that if the antithrombin was high, the prothrombin time would be relatively long, in that the greater amount of antithrombin present in the plasma would tend to delay the time of clotting on recalcifying the plasma, provided the other factors were equal. However, in comparing the prothrombin time of any given series with the antithrombin of the same series it was found that a short prothrombin time might go with the lowest or highest antithrombin. Among the diseased cases studied there are instances of even wider fluctuations than among the normals in the relation of prothrombin to antithrombin without occurrence of bleeding or thrombosis.

By Howell's theory one supposes that in normal blood the prothrombin and antithrombin are in balance which prevents intravascular clotting. It seems that there must be a relative excess of the antithrombin in the normal plasma, since considerable fluctuations may occur in the amounts of prothrombin and antithrombin without the occurrence of intravascular clotting. When blood is shed the balance is destroyed by the neutralizing effect of thromboplastic substance on the antithrombin.

By upsetting the balance of these factors, but to just what degree we cannot say, either spontaneous bleeding or thrombosis might occur. Decreases in prothrombin and increases in antithrombin are what might be expected with bleeding, with decreases of antithrombin and perhaps increase of prothrombin in thrombosis. Bleeding may of course be due to other factors of coagulation. Conditions not involving coagulation factors also cause bleeding and thrombosis.

In animals both the prothrombin and antithrombin content of the blood vary from that observed in the human being, so that their blood can not of course be used to control human, nor can serum be used as an antithrombin control to plasma since it usually contains less antithrombin than plasma.

In the normal dog numerous observations have shown that the prothrombin time varies from three to seven minutes while the antithrombin has been found to be about two and a half to three times the amount found in man. Though the antithrombin is greater<sup>10</sup> than in human blood, there is a decrease in prothrombin time which seems to indicate that the prothrombin is also increased. Here both factors are in balance but are in relatively greater amounts than in human

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<sup>10</sup> Though one speaks of antithrombin being greater in amount we cannot actually determine the amount, but its power to inhibit the action of thrombin

blood Similarly in the cat, three observations showed the prothrombin time to be six to eight minutes and the antithrombin about half again as much as in man In the rabbit the prothrombin time was from four to ten minutes and the antithrombin three times or more greater in amount than human A single observation on hogs' plasma showed a relatively high antithrombin

In considering prothrombin and antithrombin in cases one must not only consider the amounts but the relation of one to another, bearing in mind that the prothrombin test is relative Are the two factors balanced, i e, if increased are both increased, or is one increased and the other diminished?

#### ANTITHROMBIN AND PROTHROMBIN IN VARIOUS DISEASES

A study of antithrombin and prothrombin of ninety-three individuals with various diseases, making 121 observations, have been made and the results are given in the tables at the end of the paper (Tables 6 to 16)

The coagulation time of the whole blood was determined in many of the cases by a method described by Lee and White,<sup>11</sup> which is to allow 1 c c of the last blood drawn from a vein to clot in a tube 8 mm in diameter They found the normal coagulation time by this method was from five to eight minutes Our tubes were slightly larger, 9 mm, and our normals ranged from six to about eleven minutes Where figures for coagulation time are given in the tables they refer to this method During this work, larger tubes and varying amounts of blood were used, but these gave less satisfactory results for ward work Clotting took much longer owing to the larger surface area, and it was found that the tubes could not be moved at all without markedly altering the coagulation time Temperature also had a more appreciable effect Size of the needle, duration of the blood in the syringe, etc, are all factors that will vary the coagulation time When technic other than Lee and White's was used, a control from a normal case was obtained at the same time, but the results were unsatisfactory Where it was felt that there was a real decrease or increase in the coagulation time, the fact is indicated by a "+" or a "-", otherwise "N" for normal appears in the tables

If the prothrombin time was above normal, the coagulation time of the whole blood was also increased In some instances a delayed coagulation time occurred with a normal prothrombin time

(A) *Cases with Abnormal Prothrombin*—Table 4 shows the cases with delayed and accelerated prothrombin time

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11 Lee and White Am Jour Med Sc, 1913, cxlv, 495

TABLE 4—CASES WITH DELAYED PROTHROMBIN TIME

Case No	Observations	Diagnosis	Pro T minutes	Anti T minutes
92	2	Hemophilia	70-75	24 -23
83	2	Miliary tuberculosis, bleeding	39-41	14 -13
84	1	Miliary tuberculosis, bleeding	24	0 57
93	3	Benzol poisoning, bleeding	16-24	<sup>4</sup>
82	2	Amanita poisoning, bleeding	16-20	0 67-?
69	1	Pernicious anemia No bleeding	15	0 73
22	1	Pernicious anemia Thrombosis	19	0 56
88	1	Attacks of bleeding Cause (?) During no bleeding	20	14
80	1	Rheumatic purpura	17	0 87
55	1	Chronic family jaundice	20	0 80
57	2	Jaundice cirrhosis	28-14	0 55-0 55
53	1	Jaundice, pneumonia	18	0 1
		Uncinariasis		
63	1	Jaundice, cancer pancreas	18	0 78
67	1	Jaundice 5 years Cause? Bleeding	24	0 70
66	1	Congenital stenosis of bile ducts	40	

\* Antithrombin determined but once when it was 11, at which time prothrombin was twenty-four minutes

*Cases with Upper Limits of Normal for Prothrombin*

15	2	Typhoid	14	0 52-0 52
49, 50, 52	1 ea	Pneumonia	14	?-11 -11
16 and 19a	1 ea	Pernicious anemia	14	0 67-0 80

*Cases with Accelerated Prothrombin Time One Observation Each*

Case No	Diagnosis	Pro T minutes	Anti T minutes
37	Chronic myeloid leukemia, bleeding	2 $\frac{3}{4}$	0 75
36	Acute leukemia, bleeding	3	0 60
85	Acute leukemia (?) Pernicious anemia Bleeding	5	0 45
40	Chronic splenomyelogenous leukemia	4	0 46
89	Myasthenia gravis, oozing blood from gums, bad pyorrhea	4	10
81	Purpura lesions of skin Tuberculosis	4	0 66
75	Purpura lesions of skin Question of aleukemic leukemia	3	22
21	Henoch's purpura	4	0 73
73	Pernicious anemia	4	11
74	Thrombosis Syphilis	2	0 55

In some cases a prolonged prothrombin time may be explained by a corresponding increase in antithrombin, and, on the other hand, a shortened prothrombin time by a decrease in antithrombin, but as the tables show, there are cases in which a prolonged prothrombin time occurs, together with a diminished antithrombin and a shortened prothrombin time, with an increase in antithrombin. It is perhaps legitimate to conclude from this latter relation that the available supply of prothrombin in the blood, whether in solution, in the plasma, or stored in the platelets, may undergo variations in disease quite independently of the antithrombin content. The number of cases reported is too few to justify any positive deductions, but so far as they go they indicate that the supply of prothrombin was diminished in certain cases that were bleeding, as benzol poisoning, miliary tuberculosis, *Amanita* poisoning, and in certain cases of jaundice. The same is probably true in some cases of pernicious anemia and perhaps pneumonia, and in congenital hemophilia. In the latter condition, according to Howell, the prothrombin time is greatly delayed with increased or normal antithrombin content.

An actual increase in prothrombin is indicated clearly in the case of aleukemic leukemia (Case 81), but a relative if not actual increase (owing to diminished antithrombin) is shown in a number of cases, especially those with idiopathic thrombosis, some leukemias, and severe cases of typhoid fever.

Case 52 of poisoning due to fungus *Amanita phalloides* is reported in full by Clark, Marshall and Rowntree<sup>12</sup> and showed a slight delay in prothrombin time. A dog poisoned by them with this fungus showed a prothrombin time at the upper limits of normal.

(B) *Consideration of Other Factors in Relation to Prothrombin*  
1. *The Blood Platelets*—Prothrombin is perhaps largely derived from these elements of blood as has been shown by Bayne-Jones,<sup>13</sup> among others, so that if they were diminished we might expect a diminished amount of prothrombin.

Varying the number of platelets in an oxalated plasma collected with certain precautions will vary the time of clotting on recalcification, being longer the fewer the platelets (Lee and Vincent<sup>6</sup>).

Thromboplastin is also derived from the platelets, so if they are lacking and the amount of prothrombin in solution is no greater than normal, one might expect a delayed prothrombin time.

That cases with very few plates have a prolonged bleeding time and spontaneous hemorrhages has been pointed out by Duke,<sup>14</sup> yet he

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12 Clark, Marshall, and Rowntree. Jour Am Med Assn, 1915, LVII, 1230

13 Bayne-Jones. Am Jour Physiol, 1912, XXV, 74

14 Duke. THE ARCHIVES INT MED, 1912, X, 445

found by his method no striking changes in the coagulation of the whole blood

The case (79) of benzol poisoning, belongs to this group. In this case the prothrombin time fluctuated with the number of plates. It suggested that if but few plates were present the prothrombin time would be lengthened. Similar results have been obtained by Hurwitz and Drinker<sup>15</sup> in experimental benzol poisoning.

In hemophilia the plates are normal or increased in numbers and yet the prothrombin time is delayed. That the plates are fixed and rendered unavailable is suggested by Fonio<sup>16</sup>.

Among the cases with diminished numbers of plates there are both abnormally high and low amounts of prothrombin.

It thus seems that the number of plates in the blood stream does not necessarily vary the prothrombin time and perhaps they must be very few to lengthen it. They do, however, seem to be an important element in connection with spontaneous bleeding in certain cases.

2 *Calcium*—If it is necessary to add more calcium than usual to obtain the prothrombin time, one might suspect that there was something in the blood such as the bile pigments as suggested by Whipple and King<sup>17</sup> that bound some of the calcium and thus rendered it unavailable to transform prothrombin to thrombin, but we can see no reason why, if this took place, it should do so in delayed time. A case of this type is reported by Austin and Pepper and cases by Lee and Vincent<sup>18</sup>.

It is the available calcium that can act to transform prothrombin to thrombin that we are interested in from the point of view of coagulation and not the total amount in the blood.

The amount of calcium needed to obtain the prothrombin time of the normals and diseased cases was essentially the same, when the dilution of blood with the oxalate was the same, except in a very few instances which are cited below.

Of twenty observations on jaundiced cases, five cases showed a prothrombin time of over fourteen minutes and two of fourteen minutes.

Of these seven cases,<sup>19</sup> two (Cases 53 and 57) showed perhaps a tendency for, and one (Case 63) definitely, the need of an amount of

15 Hurwitz and Drinker. *Jour Exper Med*, 1915, xxi, 401.

16 Fonio. *Mitt a d Grenzgeb d Med u Chir*, 1914, xxviii, 313.

17 Whipple and King. Quoted by Whipple and Moss, see Reference 5.

18 Lee and Vincent. Personal communication, paper in print.

19 One of these seven, being Case 66, had a control with less oxalate solution, so whether more calcium was used to obtain the optimum time than would have been needed for a control, cannot be told.

calcium above that required for the controls to give the prothrombin time

Case 63, a case of prolonged obstructive jaundice, required 5 drops of calcium to obtain the optimum time when the control took but 2 or 3 drops

Of all the other cases studied no especially noteworthy changes in the optimum amount of calcium needed to clot the plasma were found except in Case 83, in which on the second observation the optimum amount of calcium was 4 drops while for the control it was 2 drops

3 *Fibrinogen*—Diminished amounts of fibrinogen can cause a loose clot and on this account perhaps favor bleeding. Whether such variations as can occur in the human body will cause an appreciable delay in the prothrombin time seems unlikely from the following facts

Fibrinogen<sup>20</sup> was determined in Cases 82 and 54, and was above normal, yet the prothrombin time was slightly delayed in one of these. In one case (57) in which the prothrombin time was 14, and in Case 56 with a prothrombin time of 8, the fibrinogen was distinctly diminished

A dog of Dr Goodpasture's and two of Dr Marshall's with phosphorus poisoning, a condition in which the fibrinogen is very low, showed on several observations a normal prothrombin time, though the antithrombin was low (0.60-0.14)

Another dog of Dr Goodpasture's with experimental pancreatic disease showed, forty-eight hours before death, spontaneous bleeding from the rectum, low fibrinogen, and the antithrombin was 0.55. The prothrombin time was nine minutes, slightly above normal for a dog. The control dog gave five minutes.

In cases of cirrhosis of the liver Goodpasture<sup>21</sup> has shown that there exists a fibrinolytic ferment which may be a cause for bleeding. The two cases studied in which this substance was detected showed a normal prothrombin time in one, and an increased time in the other, so that it does not seem as if this ferment could be a cause for abnormal prothrombin time.

(C) *Cases with Abnormal Antithrombin*—The determinations of prothrombin were followed in most instances by an antithrombin determination. If more than one control was used this is noted in the tables and the antithrombin factor is figured from their average. If the antithrombin factor of all the cases determined at the same time tended

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20 Determinations of fibrinogen when given in the table of cases were made by the drying method described by Whipple (Am Jour Physiol, 1914, *LXXXIII*, 50), normal being 350 to 600 mg per 100 cc of blood. We are indebted to Drs Marshall and Rowntree for the determinations in Cases 82, 57 and 54.

21 Goodpasture. Bull Johns Hopkins Hosp, 1914, *LXI*, 330.

to be distinctly high or low, it suggested that an unusually low or high normal had been used. If this occurred it is noted.

Excluding the cases in which the prothrombin was above 14 and below 6, we notice that sixty-two had an antithrombin factor below 1, eight had 1 and thirty-one had above 1. Therefore, in the entire group of cases an antithrombin factor of less than 1 is commoner than above 1. Perhaps any person who is ill is more apt to have less antithrombin than when well. The chances of error from the variation of normals would tend to factors higher than 1 rather than lower.

Table 5 shows the cases with increased and diminished amounts of antithrombin.

A positive increase in antithrombin content of the blood is indicated in three cases only, all of which bled, namely, one of acute splenomyelogenous leukemia, aleukemic leukemia and congenital hemophilia while a relative excess is suggested in some of those cases in which the prothrombin is apparently diminished. The coagulation time in these cases when taken showed a delay except in the case of aleukemic leukemia in which there was obviously a compensatory increase of prothrombin. The reverse condition of a distinct diminution in antithrombin content was found, especially in cases of severe typhoid fever, certain leukemias, anemias and thrombosis. In such conditions, if prothrombin and other factors are normal or perhaps increased, there should be a diminished clotting time and a tendency to the formation of thromboses. A distinct diminution of antithrombin in some cases that bleed may be a compensatory effect due to the bleeding from causes other than antithrombin or prothrombin.

Fifteen cases of typhoid fever, on which twenty-four observations were made, were studied especially with the thought that some of them would develop a thrombosis, and that one might be able to predict such an occurrence by a decrease in the amount of antithrombin. Fortunately for the patients' sake none of the cases developed a definite thrombosis.

Low factors frequently occurred, the lowest in the two sickest cases. The two highest occurred in mild cases in which the temperature was normal or nearly so.

All the antithrombin factors of the nineteen cases grouped in the tables under secondary and pernicious anemia are below 1, except in one case of pernicious anemia which had 1.2 and a prothrombin that was abnormal (four minutes) and Case 34 of secondary anemia with frequent hemorrhages. There are ten cases with factors below 0.75, six of which are from the eight cases of pernicious anemia. Nearly all the cases that had a distinct anemia and a normal prothrombin, tend to have a low antithrombin. There are, however, exceptions.

TABLE 5—CASES HAVING ANTITHROMBIN BEYOND THE CONCEIVABLE LIMITS OF NORMAL

*Cases Having Antithrombin Below 0.55*

Case No	Diagnosis	Pro T minutes	Anti T minutes
73	Thrombosis, idiopathic (?)	2	0.55
67a	Prolonged jaundice, recently bleeding	10	0.54
57	Jaundice, cirrhosis, two observations	28-14	0.55-0.55
15	Typhoid, very sick, purpura, three observations	14, 14, 9	0.52-52-53
40	Splenomyelogenous leukemia, chronic	4	0.46
8	Typhoid, purpura, 48 hrs before death	12	0.46
85	Pernicious anemia (?), acute leukemia, bleeding	5	0.45

*Cases Having Antithrombin Above 1.81*

41	Acute splenomyelogenous leukemia, very slight bleeding, two observations	10-10	2.4 -1.9
81	Aleukemic leukemia (?), purpura	3	2.2
92	Hemophilia	75-70	2.4 -2.3

*Cases with Antithrombin 0.68 or Below*

1, 2, 5b, 13 15b and 15e 17, 18, 19a 69, 20 74, 75b and c 29, 30, 32 58 68 36 82 84	Typhoid, five cases Pernicious anemia, one with thrombosis, five cases Purpura, anemia, two cases Secondary anemia, three cases Jaundice, endocarditis, anemia, infarcts Thrombosis, traumatic after leg amputation Acute leukemia Amanita poisoning, bleeding Miliary tuberculosis, bleeding	6-11 8-19 8-14 6-12 10 10 3 20 24	0.57-0.67 0.56-0.67 0.60-0.66 0.57-0.65 0.61 0.67 0.60 0.67 0.57
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*Cases with Antithrombin 1.47 or Above*

12 61a, 61b, 65 47, 44 78	Mild typhoid Jaundice, two cases, long duration in one, the other catarrhal Positive Wassermann, two cases, one with large liver and nephritis, the other showed only fever Purpura, dyspituitarism	9 6-8 12-6 8	1.8 1.7 -1.8 1.64-1.73 1.78
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Drinker<sup>22</sup> has shown that with rapid progressive hemorrhage in animals the antithrombin falls and two observations on animals made by us have shown the same. In Case 10, whose hemoglobin was 80 per cent and fell in four days to 30 per cent from hemorrhage, the antithrombin at this latter time was 0.96, but what it was previously we do not know. We might have expected it to be low from the anemia as well as from the sudden loss of blood.

Among the miscellaneous cases the average antithrombin is over 1, as a contrast to the anemias. Some of these cases were studied because of enlarged livers, in view of the fact that the liver is important in the formation of antithrombin.<sup>23</sup> Among the clinical cases, however, we have many types of liver disease with antithrombin varying from 0.55 to 1.7, and no definite relationship can be seen between the different liver conditions and the amount of antithrombin.

Does antithrombin vary with the amount of fibrinogen? In anemia the fibrinogen is often low (Whipple<sup>20</sup>) also in typhoid (D'Oelsnitz et al.<sup>24</sup>) as is the antithrombin. In the dogs with phosphorus poisoning and in Dr. Goodpasture's dog with pancreatic disease, both the fibrinogen and antithrombin were low. Case 56, with a low fibrinogen, had antithrombin 1.1. In Case 54 of pneumonia with increased fibrinogen, antithrombin was normal. Whether antithrombin usually falls with diminution in the amount of fibrinogen, we have not enough data at present to say.

Syphilitic serum has been shown by Hirschfeld and Klinger,<sup>25</sup> also Frankel and Thiele<sup>26</sup> to have the power when mixed with proper amounts of coagulation materials to inhibit coagulation. This, however, is probably not due to antithrombin, as none of the five cases in our series with a positive Wassermann showed any special variation from normal.

Dochez<sup>27</sup> has made a careful study of the coagulation time in pneumonia and found it increased at the height of the disease and suggested that it was due to an antithrombin increase. Actual antithrombin increase did not exist in the two cases of pneumonia studied, the factors in both were 1, while the prothrombin was well at the upper limits of normal, so there may have been a slight relative increase.

(Studies at the Massachusetts General Hospital are now being made on the factors of coagulation in pneumonia and will be reported at a later date.)

22 Drinker, K. R. and C. K. *Am Jour Physiol*, 1915, xxvi, 305.

23 Denny and Minot. *Am Jour Physiol*, 1915, xxxviii, 233.

24 D'Oelsnitz, et al. *Bull de l'Acad de med*, Paris, lxxiii, 282.

27 Dochez. *Jour Exper Med*, 1912, xvi, 693.

25 Hirschfeld and Klinger. *Deutsch med Wchnschr*, 1914, xl, abstr. of Am Med Assn, 1914, lxxiii, 1241.

26 Frankel and Thiele. *Munchen med Wchnschr*, 1914, lvi.

## CONSIDERATION OF THE FINDINGS IN CERTAIN GROUPS OF CASES

Kocher,<sup>28</sup> Kollman and Godsky<sup>29</sup> and others have reported changes in the coagulation time of the blood in thyroid disease. Two cases of Graves disease studied, not included in this series, showed no very striking changes in their prothrombin and antithrombin content.

Howell<sup>1</sup> found no abnormality in the prothrombin or antithrombin content of the blood in the cases of purpura which he studied, and we found no significant changes in our cases, except in two (Cases 78 and 81) the antithrombin was distinctly high, in one the prothrombin time was normal, and in the other decreased. Whether the increased antithrombin could have been the cause for the purpura in these two cases can only be told after further research on the amount of antithrombin in relation to prothrombin that may cause bleeding.

Among the leukemia cases high prothrombin (decreased prothrombin time) frequently occurred. In some of the leukemias this might be due to the increased number of white cells in the circulation which yield thromboplastic material, but some of the cases with an equal or greater number of cells had a normal prothrombin time.

The white cells from Case 41, with antithrombin 2.2, were isolated and tested to see if they showed any antithrombic activity, but none was found. These cells, like any white cells, exhibited thromboplastic activity.

In three cases of spontaneous thrombosis Howell found that there was a low antithrombin with a normal prothrombin. The antithrombin in his cases expressed as antithrombin factors vary from 0.3— to 0.4—.

One case (73) of idiopathic thrombosis gave a low antithrombin factor (0.55) but also the highest prothrombin of any case, two minutes. A case of pernicious anemia without fever, developing thrombosis after splenectomy, gave a low antithrombin, 0.56, slightly lower than the other cases of pernicious anemia, with a low prothrombin (19 minutes). The serum of this case at necropsy was tested for antithrombin and found to be 0.4 (normal oxalated plasma as control). We do not know how serum obtained at necropsy may vary from normal blood in its antithrombin content. Serum as a rule has slightly less antithrombin than oxalated plasma. One case of cardiac disease whose serum was tested about the same time after death as that of the pernicious anemia case, gave a factor of 0.9. It thus seems that the serum from this pernicious anemia case after death contained certainly less antithrombin than serum of a patient whose antithrombin was presumably normal before death.

28 Kocher Arch f klin Chirurg, 1912, xcix, 280

29 Kollman and Godsky Ztschr f klin Med, 1914 lxxix, 362

The other cases of thrombosis studied were probably not of the idiopathic type. The antithrombin in these varied between 1.46 and 0.67.

It is quite possible that none of the cases we have studied is of the same type as those studied by Howell, and until we know more about such cases we cannot tell what type it is that has a strikingly low antithrombin content.

Cases with quite wide changes in the prothrombin and antithrombin content from normal and in the relation of these two substances to each other, may or may not bleed. All cases with spontaneous bleeding are not due to these factors.

Of the cases studied with spontaneous bleeding and hemorrhagic tendency, if the factors were abnormal at all, there was usually a decrease of prothrombin, with more usually the antithrombin factor above than below 1. The few cases with strikingly high antithrombin content all had some signs of spontaneous hemorrhage.

Cases of bleeding occurred with increased prothrombin and with antithrombin above or below 1. In such instances perhaps there were other factors at work to cause the bleeding and the increased prothrombin was a compensatory process to shorten the coagulation time and stop the hemorrhage.

#### SUMMARY AND CONCLUSIONS

1 Prothrombin time, tested by the method used, varies normally from six to fourteen minutes.

2 Technic and difficulties of the antithrombin test have been described.

3 The antithrombin factor is the most satisfactory method for the comparison of amounts of antithrombin.

4 Antithrombin varies normally. The antithrombin factor must be below 0.55 and above 1.81 before one can be absolutely sure that the amounts are abnormal, one may be reasonably sure that the amounts are abnormal if the factors are below 0.68 or above 1.47.

5 In some cases a prolonged prothrombin time may be explained by a corresponding increase of antithrombin and a shortened prothrombin time by a decrease. There are cases which suggest that the available supply of prothrombin in the blood may undergo wide variations in disease independent of the antithrombin content. Certain cases of bleeding and of jaundice, also hemophilia, as well as others, seem to have a diminished supply of prothrombin. Actual increase of prothrombin does occur, as is indicated in a case of aleukemic leukemia, and in some animals as compared to the human being. Relative increase is shown in a number of cases, especially thrombosis and some leukemias.

6 Prothrombin time does not always vary with the platelet count

7 Cases exist in which more calcium than usual is needed to obtain the prothrombin time

8 The amount of fibrinogen in human blood probably does not vary sufficiently to alter appreciably the prothrombin time

9 A positive increase of antithrombin is indicated in three cases. A relative excess is suggested in some cases in which the prothrombin is apparently diminished. Diminution in antithrombin was especially found in cases of severe typhoid fever, certain leukemias and anemias and thrombosis, and in some cases associated with a low fibrinogen content.

10 Cases of spontaneous bleeding occurred with normal coagulation factors. Others showed a low prothrombin, usually but not always associated with a relatively high antithrombin. The three patients with a very high antithrombin, all bled.

Since this article was written Hurwitz and Drinker have published (*THE ARCHIVES INT MED*, 1915, xv, 733), a paper entitled "Factors of Coagulation in Primary Pernicious Anemia." While we found an abnormal antithrombin content in our cases of pernicious anemia, they did not. This may be due to differences of technic. They state, "Prothrombin is diminished slightly in all cases of pernicious anemia." Our findings agree, with the exception of two cases, in which there was an increase.

It is a pleasure to thank Dr. Howell for his supervision of this work and to thank the members of the staff of the Johns Hopkins Hospital for allowing us to study their cases.

188 Marlboro Street—285 Marlboro Street

#### TABLE OF CLINICAL MATERIAL

Cases from the wards of the Johns Hopkins Hospital, except the following. No. 83 was at Bay View Hospital and Case 30, one of Dr. Boggs', to whom we are indebted for the opportunity to study these two cases.

Cases 27, 85 and 86 were private patients of Dr. Thayer.

Cases 67, 88 and 91 were seen by Dr. Howell in consultation.

Case 37 was one of Dr. Judd's, reported in *Jour Am Med Assn*, 1915, lxiv, 1630.

We are much indebted to Drs. Thayer, Howell and Judd for being able to study the above cases.

The blood from the patients was obtained by one of us in all instances except Case 37, which was obtained for us with our materials by Dr. Judd.

The date refers to the year March 30, 1914 to March 29, 1915, unless 1915 is stated.

The clots of the whole blood retracted unless stated.

Platelet counts were done by Wright and Kinnicutt's method.

TABLE 6—TYPHOID FEVER

Proved by positive Widal's or blood cultures All these cases had a hemoglobin of over 80 per cent, unless stated

No	Date	Week of Disease		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
1	June 10	3	Fever began to break June 13 Perforation of bowel occurred June 20 Fever up to 101 F, until death, July 20	8	1 0		6
1a	June 27	5		8	0 67		8
2	July 13	3	Mild case Fever began to break July 16 Uneventful convalescence except for slightly tender toes	6	0 63	N	6
2a	July 20	4		8	0 70	SI—	6
3	July 22	3	Fever began to break July 30, July 25-30, hemorrhages, small, from bowel	6	0 81	N	6
4	Oct 16	9	Normal temperature after October 16 Discharged November 13, after uneventful convalescence	8	1 15		10
5	Oct 21	3	Fever begins to break October 24, but reaches to 105 F, not being normal till November 22 No complications	8	1 15		10
5a	Oct 23	4		6	0 75	5½	8
5b	Nov 11	7		8	0 65		12*
6	Oct 28	3	Hemoglobin, 63 per cent, R C, 3,712,000 Fever began to break November 3 Temperature close to normal, Nov 20-30, then a relapse until December 20 No clot retraction	10	0 57	10	9-12†
7	Oct 28	3	Fever begins to break November 2-7, running up to 100.5 F until Dec 22	10	0 74	8	9-12‡
8	Oct 29	3+	Severe toxic case, October 24 urticaria and purpura appeared, growing worse until death, October 30 No necropsy, plates plentiful in smears	12	0 46—	6+	8
9	Nov 23	4	Perforated November 20, died November 24 Fever 101-103 while in hospital	8	0 85	5	14

10	Oct 14	2+	October 10, 1,000 cc rectal hemorrhage, several smaller hemorrhages until October 14, hemoglobin in five days reduced from 80 to 30 per cent Mild relapse October 27-November 4, without further complications Mild case Temperature 100 F after October 18, and normal after October 27 Uneventful case Temperature normal January 8 and low after December 17 Fever high until November 19 Relapse December 1, at which time a question of peritonitis was raised, discharged well January 1	8	1 1	6½	12 ‡
11	Oct 16	5	Mild case Temperature 100 F after October 18, and normal after October 27	6	1 0		10
12	Dec 17	3	Uneventful case Temperature normal January 8 and low after December 17	9	1 80	7	14 §
13	Nov 9	3	Fever high until November 19 Relapse December 1, at which time a question of peritonitis was raised, discharged well January 1	10	0 57		8
14	Dec 9	3	Mild case R C, 6,664,000 No fever after December 16	8	0 92	8	8 ¶
15	Oct 14	3	Husband of No 6 Rectal hemorrhage, October 15 and 18, reducing hemoglobin 10 per cent	14	0 52	11½	12 ¶
15a	Oct 21	4	October 22, sloughing decubitus developed, others occurred later	14	0 52	10	10 ~ +
15b	Nov 6	6	November 4 Arms became swollen and urticaria developed	10	0 64	8	10
15c	Nov 11	7	Question of axillary thrombosis was raised, left arm worse than right	9	0 53		6-11 † †
15d	Nov 18	8	Purpura of arms and face developed, November 6, increased by tourniquet	11	1 00		8-12 † †
15e	Dec 9	11	Urticaria and slight purpura persisted with fluctuations until November 15, accompanied with and followed by scaling of skin all over body Fever reached normal, November 6, gradually rose again until November 14, then slowly fell to 100 by December 9, and fluctuated near normal until discharge Acute nephritis developed in December	11	0 65		13-9 ¶

\* Six controls † Two controls ‡ Two controls § Other cases run with this had antithrombin 1 3 and 1 15 ¶ Four controls  
 † Two controls that were equal in antithrombin content  
 † † Six controls ‡ † One of controls of October 14 Other cases had high antithrombin

All have typical blood smears

No	Date	Red Count	Hgb (Sahli) Per Cent		Pro- thrombin	Anti- thrombin	Coagula- tion Time minutes	Pro- thrombin Control minutes
16	May 13	4,640,000	75	Bad pyorrhea No fever Spleen not felt	14	0.80	N	12
17	July 6	1,900,000	42	Bad pyorrhea Slight fever Spleen easily felt	10	0.60	N	10 <sup>+</sup>
18	July 13	626,000	25	Continued fever often 103 F Died Sept 2	8	0.62	N	6
19	July 20	1,000,000 (Decreased fra- gility of red cells)	25	Continued low fever Combined sclerosis of cord	8	0.72	8	6
19a	Nov 18	1,608,000	33	Nov 14, transfused 500 cc Highest red count Nov 19, 1,608,000, with blast crisis	14	0.67	17	9-12 <sup>+</sup>
20	Oct 17	1,872,000	35	Large spleen No fever	10	0.65	5	8
21	Dec 2	2,080,000	55	Numbness hands and feet Large spleen Slight fever	4	1.2		11-14 <sup>+</sup>
21a	Dec 2				4			
22	Dec 12	1,584,000	37	Very slight fever Spleen felt (poor clot retrac- tion)	15 <sup>+</sup>	0.73	10 <sup>+</sup>	7 §
23	Oct 21	1,312,000 (Slightly increased fragility of reds)	33	Liver and spleen easily felt Question of myxedema Question of family jaundice (Labor, Oct 4) Note also Cases 69 and 85	10	0.73	9	10

\* Three other cases had antithrombin over 1 † Six controls ‡ Two controls § Two other cases had prothrombin of twelve and eight minutes

TABLE 8—SECONDARY ANEMIA

No	Date	Red Count	Hgb (Sahl) Per Cent		Pro- thrombin	Anti- thrombin	Coagula- tion Time minutes	Pro- thrombin Control minutes
24	May 11	2,438,000	25	Cancer of stomach Advanced case White count 8,000	8	0.84	SI +	8
25	June 8	4,112,000	40	Positive Wassermann Osteomyelitis of rib, culture showed paratyphoid organism Very large spleen White count 4,000	6	0.95	8	6
26	July 22	?	65	Congenital cystic kidneys Chronic nephritis Nosebleed frequent for eight years Fever 99-101 F	8	0.90	N	6
27	July 21	1,700,000	25	High fever, very large spleen, liver palpable Diagnosis (?)	10	0.85	SI +	6
28	Dec 2	4,184,000	80	Banti's disease with ascites	11	0.80	11	11*
29	Oct 19	1,812,000	36	Long standing anemia due to possible anaplasma in blood White count 19,450	10	0.65	7	10†
30	Oct 23	2,824,000	40	Severe chronic nephritis Albuminuric retinitis Uremia Myocardial insufficiency Discharged improved January 13	12	0.57	11	8
31	May 22	4,000,000	65	Hodgkins' disease with marked enlargement of mediastinal nodes	10	0.90		6‡
32	July 9	4,100,000	72	Aneurysm, thoracic aorta, positive Wassermann Myocardial insufficiency, ascites Systolic blood pressure, 0.90	6	0.65		8
33	Oct 9	?	70	Syphilis of central nervous system	10	0.75	9	6
34	Feb 22	2,500,000	40	Frequent small hemorrhages from nose Diagnosis Note other cases of secondary anemia under purpura, leukemia, etc	12	1.31	?	6

\* Two controls † Three other antithrombin were 11, 18 and 13 ‡ Two other cases of prothrombin were (1) eight and (2) ten minutes



No	Date	Red Count	Hgb (Sahl) Per Cent	White Count		Pro- thrombin	Anti- thrombin	Coagula- tion Time minutes	Pro- thrombin Control minutes
35	Dec 17	2,856,000	50	930,000	Fairly acute spleno- myelogenous with fever	9	12	SI +	14
36	Nov 17	?	80	7,000	Ninety per cent small lymphocytes acute type	3	0.60	—	8-12
37	Dec 12	1,000,000	30	300,000	Acute myelogenous died of hemor- rhage, Dec 14 See under "Bleeding Cases"	2¾	0.75	-	7
38	May 22	2,792,000	54	352,000	Chronic splenomye- logenous	8	10	N	6
39	July 6	4,430,000	68	368,000	Chronic splenomye- logenous Devel- oped hemorrhagic purpura in Septem- ber and died	10	10	N	10
40	July 20	2,320,000	47	187,200	Chronic splenomye- logenous with arteriosclerosis	4	0.46	—	6 +
41	April 29	2,880,000	50	362,000	Acute splenomye- logenous High fever Slight bleed- ing from nose Question of bleed- ing to internal ear No further bleed- ing before patient left hospital	10	24	?	6†
41a	April 30	2,880,000	50	362,000	Note also Cases 81 and 85	10	19‡		6

† Six controls    ‡ One other case antithrombin = 13    § One other case antithrombin = 12

TABLE 10—MISCELLANEOUS

Hgb over 80 per cent unless stated

No	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
42	June 4	Chronic nephritis, chronic alcoholism Large liver Myocardial insufficiency, arteriosclerosis, ascites, liver with slight passive congestion at autopsy Hgb 73 pct Positive Wassermann Chronic nephritis, arteriosclerosis Myocardial insufficiency, with large liver Red count 6,600,000 Hemoglobin 95 per cent Myocardial insufficiency with liver to umbilicus Dilated aortic arch Aortic and mitral disease Typical angioneurotic edema with urticaria Positive Wassermann Fever to 102 F for two weeks, gradually reaching normal July 10 White count 4,300	6+	11	N	8
43	July 9		8	071	N	8 <sup>+</sup>
44	Oct 19		12	164	8	10†
45	Oct 21		10	130	9	10
46	May 1	Arteriosclerosis Sinusitis Chronic nephritis (?) Positive Wassermann Consolidation of lower right lobe of lung, perhaps pneumonia, thought to be tuberculosis No crisis Discharged against advice when temperature was still 99-102 F Lobar pneumonia, typical crisis October 16 Preeclamptic Delivered of premature baby this morning In past four days has had 2-3 convulsions Bled 500 c c this morning	8	10	N	14
47	July 6		12	17	SI +	10‡
47 <sup>a</sup>	July 7		10	12	N	10
48	Dec 9		10	085	N	9-13§
49	Oct 19		14	11	10	10¶
50	Oct 13		14+	11	14	10
51	Jan 13		6	10	5	6

\* Three other cases have low antithrombin † Case 29 had antithrombin 0.65 ‡ Case 17 had antithrombin 0.60 and Case 59, 17  
 § Four controls ¶ Other prothrombin times, 8-12

TABLE 11—JAUNDICE  
(A) SLIGHT

Hemoglobin over 80 per cent unless stated

No	Date	Remarks on Blood	Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
52	April 22	W C, 23,160	14	9	+	6*
53	May 12	R C, 4,000,000, hgb, 40 per cent, W C, 4200 Plates normal in smears	18	10	15	12
53a 54	June 1 Oct 28	W C, 15,680 hgb, 65 per cent Fibrinogen, 700 mg per 100 cc blood	8 12	00 000	N 13+	6 0.127
55	March 30	R C, 2,820,000, hgb, 55 per cent Plates in smears appear normal	20	(80)	+	8
55a 56	May 29 Oct 9	1 hgb, 80 per cent W C, 11,700 Fibrinolytic ferment present Fibrinogen diminished 280 mg per 100 cc Fibrinolytic ferment present	10 8	11 11	7	8 0
57	Nov 23	1 hgb, 80 per cent W C, 11,700 Fibrinolytic ferment present	28	055	15+	11
57a	Dec 2	Fibrinogen, 211 mg per 100 cc	14	055	12+	11-127
58	Oct 14	R C 3,100,000, hgb, 64 per cent, W C, 21,000	10	061	9	127

Lobar pneumonia Positive Wassermann Crisis, April 23  
Positive Wassermann Uremia  
Bronchopneumonia Large spleen  
Bradycardia Fever to 105 F on the 12th and 13th Crisis 13th Jaundice gone May 23

Lobar pneumonia Liver, October 27-30 Liver large

Congenital family jaundice Liver on legs Slight jaundice

Almost no jaundice present  
Congenital Atrophic cirrhosis of liver Arteriosclerosis Died "hepatic insufficiency," October 28

Cirrhosis of liver Plates appear in normal numbers in smears Very little jaundice now

Acute and chronic endocarditis Broken compensation with ascites Pulmonary infarcts Fever 100-101 F till October 20

(B) MODERATE JAUNDICE

59	May 25	W C, 17,000	Catarrhal jaundice, age 10	6	075	N	8
60	Oct 23		Catarrhal jaundice, age 17	6	074	7	10
61	July 6		Catarrhal jaundice, age 21	6	17	N	10†
61a	July 7		Jaundice gone by July 22	8	18	N	8
62	July 9		Myocardial insufficiency Chronic nephritis Liver large	8	070	N	8

(C) DEEP JAUNDICE

63	May 29		Cancer of head of pancreas Meta- stasis to liver (?) Duration weeks	18	078	SI +	6
64	June 10	R C, 4,100,000, hgb, 42 per cent	Cancer of stomach with liver meta- stasis Fever up to 100 F	6	093	—	6
65	March 18	R C, 3,400,000, hgb, 72 per cent, W C, 7,500	Stenosis common bile duct due to stone proved at operation, March 20 Jaundice for five years with short periods of relief Began to bleed from gums three days after operation, developed peritonitis from which he died, March 27, bleeding from nowhere else and was not severe	6	173	19	6
65a	March 24		Congenital stenosis bile ducts Baby	12	10 +	21	9
66	March 11		Woman, aged 29 Jaundiced for	40			8
67	Feb 25		seven years, has been operated on for gallstones, none found, one year ago bled badly when tooth pulled, two months ago bled from gums for about two weeks, bleed- ing has now been going on one week and bleeds when she scratches herself	24	070	28	8
67a	March 15		Given kephalin for the past two and one-half weeks, no bleeding for ten days	10	054	14	6
67b	April 1		No kephalin for past two weeks and now bleeding a little from gums	12	10	18	6
	May 18		Less jaundice No kephalin since last note No bleeding	15	08	23	8

\* No other cases † Two controls ‡ 67b antithrombin, 0.60

TABLE 12 — THROMBOSIS

Hemoglobin over 80 per cent unless stated

No	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
68	1914 Oct 9	Of femoral artery and vein, traumatic etiology After amputation of leg patient died three days later Pernicious anemia, splenectomy Nov 11 Thrombosis of femoral vein recognized for eighteen hours Nov 17, red blood cells, 3,465,000, hemoglobin, 75 per cent, plates very plentiful in smears after splenectomy Patient died from pulmonary embolus Nov 30 Confirmed at necropsy, which showed thrombosis, also thrombosis of femoral, splenic, portal veins and inferior vena cava Combined sclerosis of cord Pernicious anemia There was no fever from November 11 to November 29 "Blood" five hours after death fluid due to autolysis, as it would clot only on addition of solution of fibrinogen This "blood" diluted with oxalate is what was tested, the control being normal blood diluted with oxalate as usual	8	1 46	6	6
68a	Oct 16		10	0 67	5	10
69	Nov 24		19	0 56		14
69a	Nov 30			0 40		
70	1915 Jan 15	Private case, Dr Boggs Frequent attacks of idiopathic thrombosis No attack for over six months 0 0001 gm of hirudin given intravenously after blood drawn Temperature 105 F, severe reaction, well in forty-eight hours	7	1 30	8	8
70a	Jan 16	General paresis Salvarsan intravenously five days ago Intraspinal mercury albuminate yesterday, today evidence of venous thrombosis of femoral vein	9	1 25		9
71	Jan 16	Operated for inguinal hernia three weeks ago, about ten days ago developed cough with bloody sputum, pain in chest, bronchopneumonia infarct (?)	11	1 0	8	9
72	Jan 13	Idiopathic thrombosis, began with a femoral thrombosis two weeks ago, then cerebral Comatose	8	1 30	6	6
73	April 17		2	0 55	?	8

TABLE 13—PURPURA WITH SKIN LESIONS

No	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
74	1914 May 8	Hgb, 50 per cent, W C, 10-15,000 R C, (?)	Normal in smears	Generalized tuberculosis of sixteen months duration Fading purpuric spots on legs	4	0.66		8
75	June 1		June 3 180,000	Henoch's purpura with recurring abdominal attacks and lesions on skin	4	0.73		6
75a	June 4			Many spots gone Angioneurotic edema at times	6	0.72	N	8
75b	July 6	Hgb, 70 per cent, R C, 4,300,000	150,000	Fresh crops of spots fourteen hours ago	8	0.60	N	10 +
75c	Oct 13		60,000	Abdominal attack and many fresh minute spots all over body (Poor clot retraction)	8	0.63	8	10
76	Oct 2	Red cells, 4,080,000 Hgb, 55 per cent	240,000	Male, 62 years of age Lymph glands and spleen enlarged Chronic diarrhea, achylia gastrica, continued low fever for two years Very frequent outbreaks on his legs of purpuric spots, spots, present October 2, fresh crop Oct 29	10	0.71	8	10

TABLE 13—PURPURA WITH SKIN LESIONS (Continued)

Hemoglobin over 80 per cent unless stated All clots retract well

No	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
77	Dec 12		Plentiful in smear	Chronic nephritis with albuminuric retinitis, mild uremia Purpuric spots on legs developed, December 11	12	070	9	7
78	July 7		A p p e a r normal in smears	Female with male characteristics Dyspituitarism Cyst of thyroid Blood pressure, systolic 180 Frequent attacks of epistaxis and small purpuric spots on arms, present July 7 Female giving history of repeated attacks of purpuric spots on skin None present June 8 Rheumatic purpura, child, spots nearly gone	8	178		8†
79	June 8				6	12	N	6
80	March 11 1915	?	?		17	087		?
81	April 21	A high percentage of large lymphocytes W C, normal	?	Big spleen Question of aleukemic leukemia Has had several attacks of purpura and has one at present	3	22	9	6
				Note also Cases 8 and 15				

\* Case 59, antithrombin, 17 Case 46, 17 † Other cases antithrombin 11 and 180

SPOTS ON SKIN

TABLE 14—HEMORRHAGIC CASES WITHOUT PURPURIC SPOTS ON SKIN

No	Date	Blood	Plates	Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
82 <sup>r</sup>	Oct 2	R C, 6,456,000 Hgb, 90 per cent W C 16,720 Fibrinogen, 600 mg per 100 cc	388,000	20	0.67	12	10
82 <sup>a</sup> 83	Oct 3 Dec 2	Hgb, 30 per cent R C, 1,500,000	Plates 60,000 appear diminished in smears but not absent	16 44	13	11 35	8-10 <sup>+</sup> 11-12 <sup>+</sup>

Poisoning from the fungus *Amantia phalloides*, eaten about September 14. September 28 bleeding from gums began, continued intermittently until death. Bleeding from rectum began October 7, continued intermittently till death, October 11. Functional kidney tests showed diminished function of kidney. Autopsy showed central necrosis of liver, epithelial necrosis of kidney, acute enteritis and colitis hemorrhagic bronchopneumonia.

Bleeding from nose, rectum and genito-urinary tract which began about November 25 and persisted until death about December 12. Autopsy showed miliary tuberculosis with enlarged liver. After the blood clotting it would recede on breaking up several

\* Case reported by Clark, Marshall and Rowntree



TABLE 14 —HEMORRHAGIC CASES WITHOUT PURPURIC SPOTS ON SKIN (Continued)

No	Date	Blood	Plates		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
83a 84	Dec 9 Feb 22	R C, 3,200,000 Hgb, 60 per cent	112 000 ? W C 6,600	At necropsy, miliary tuberculosis. Duration 2+ months. At onset, severe nosebleeds, persisting off and on until death about February 28.	39 24	14 0.57	30	9-13 $\frac{1}{6}$
85	1915 April 21	R C, 1,500,000 Hgb, 30 $\pm$ per cent W C, (?)	?	Splenectomy one month ago for aplastic anemia with marked improvement until severe bleeding of nose began a few days ago, now thought to be acute leukemia. No record if clot retracted or not.	5	0.45	6	6
37	Dec 12	See under leukemia	Plates absent in smears	Acute lymphatic leukemia of six weeks' duration. December 6 began to have oozing nosebleed which persisted. December 10, hemorrhage from stomach and rectum. Direct transfusion from donor of same isoagglutinin group after specimen obtained for testing coagulation, but hemorrhages persisted and patient died December 13.	2 $\frac{1}{4}$	0.75	"	7 $\frac{1}{8}$

41	April 29	See leukemia				10	24	?	6
41, 86	April 30 July 15	Hgb, 70 per cent	Normal in smears		Acute leukemia, slight nose-bleed and question of bleeding to internal ear	10	19 078	N	8 6+
87	March 5	'Normal'	?		Prolonged oozing of blood from nasopharynx after operation Trauma right hand two years ago, since then intermittent hemorrhagic swelling of area every two to three weeks No other hemorrhage No hemorrhage for two months, during this time has had cephalin, but also a splint	11	123	14	7
88	April 6		Plates (?)		No hemophilic history, age 24 (?) Was well until after operation on tonsils one year ago, when he nearly bled to death Has bled very severely several times since Last, two months ago No anemia now or bleeding No record if clot retracted or not	19	14	20	6
89	July 13	Hgb, 100 per cent	Plentiful in smears		Myasthenia gravis, mild oozing from gums, with bad pyorrhea	4	10	6	6¶
90, 91	June 8 Oct 28	Normal	?		Large hematoma on leg Traumatic Gives a history of bleeding easily and for rather long time if cut Not evident October 28	8 12	090 10	N 9	6 12

† Four controls    ‡ Two controls    § Case 69, prothrombin, twelve minutes    Case 22, fifteen minutes    ¶ Three other cases had prothrombin time 5.18 to eight minutes

TABLE 15—HEREDITARY HEMOPHILIA

No	Date		Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Pro-thrombin Control minutes
92	Oct 9	Case of Joseph Y, previously studied by Dr Howell When prothrombin on several observations in spring of 1913 was five hours to three hours and ten minutes For past weeks has been having kephalin by mouth Entered hospital October 6 on account of sharp pain and swelling in groin, believed due to hemorrhage into iliac muscle Discharged October 29 with swelling and pain gone Up to October 17, temperature 99-100 F Oct 9, white blood cells, 16,680, red blood cells, 3,992,000, hemoglobin, 80 per cent Blood smears showed diffuse basophilua of reds, slight anisocytosis, differential count normal, plates plentiful Clot retracts well Plates 300,000 October 15	75	24	80	6
92a	Oct 15		70	23	85	10

## BENZOL POISONING

CASE 93—Case of severe purpura hemorrhagica due to poisoning by benzol Entered May 2 with bleeding from gums and nose and purpuric spots all over body and retinal hemorrhages Red blood cells, 1,460,000, hemoglobin, 25 per cent, white blood cells, 1,500 Bleeding time fourteen and one-half minutes Purpuric spots were first noticed about April 1

May 3, 14, 17, 23, 31 and June 13, she received transfusions of blood, following each she improved distinctly, and the bleeding time would become two to three minutes, having been twenty-four to eight minutes before transfusion Though improved after the transfusions, a relapse would set in with bleeding from gums and nose and fresh purpuric spots on the skin However, after June 13 there was no more bleeding, except for a slight amount from the gums June 24 to 29 Kephalin solution applied locally to gums and also pure thrombin solution seemed to temporarily check bleeding

The red count reached 1,971,000 with hemoglobin 48 per cent, May 17, after transfusion, and fell as low as 696,000 with 11 per cent hemoglobin, May 31, before transfusion, reaching 1,680,000, with hemoglobin 53 per cent, June 4, and 4,528,000, with 65 per cent hemoglobin, June 14, and July 26 3,128,000 and hemoglobin 67 per cent In October she appeared quite healthy, with hemoglobin 80 per cent and plates plentiful in blood smear

Plates Almost none seen in smears May 9, count = 8,400, on May 31, 10,000 More plates in smears on June 2 than May 31, but distinctly scant On July 22 they were 170,000

TABLE 16—BENZOL POISONING

No	Date	Pro-thrombin	Anti-thrombin	Coagulation Time minutes	Control Pro-thrombin minutes
93	May 3— Before transfusion	24	11	Slight + no retrac of clot	12
93 a	May 31— Before transfusion on this day	26	—	Not done	10
93 b	June 2	16	—	Not done	8
93 c	July 22	12	—	Not done	8

# SOME CLINICAL, PHYSIOLOGIC AND CHEMICAL OBSERVATIONS ON PTOMAIN POISONING FROM "CREAMED" CODFISH<sup>1</sup>

M A BLANKENHORN, M D, G E HARMON, M D

AND

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CLLVILLAND

On April 24, 1915, about eighty patients in the general wards and a number of the help in the kitchens of Lakeside Hospital were seized with alarming gastro-intestinal symptoms in one and a half to three hours after eating the evening meal with which had been served "creamed" codfish<sup>1</sup>. It was definitely ascertained that the various individuals became ill as a result of partaking of the fish. Some of the material was obtained, and it seemed worth while to make some physiologic, bacteriologic and chemical observations with it because of general medical and scientific interest in the subject of ptomain poisoning which was suspected.

Symptoms arising from "ptomain poisoning" are attributed to numerous causes. Among the more popular are (1) gastro-enteritis due to bacterial infection, (2) effects of toxic chemical substances elaborated by bacteria, and (3) bacterial infection and toxic substances combined. Finally, there are those who place little faith in any of these explanations and prefer to disbelieve ptomain poisoning altogether. Recent investigations on a number of toxic bases which occur in and can be prepared from putrefied flesh and certain vegetable drugs, such as ergot, would seem to indicate that these might be concerned in ptomain poisoning. The effects of a number of these bases have been studied systemically and on surviving organs. An attempt was made to study the effects of our material in this direction. The chemical identification of the active substances is difficult, but the properties of a number of the bases are now well known. This has also been attempted in a general way with our material.

No claim to originality for either the methods or ideas here presented is made. However, the mode of treatment used, it is believed,

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\* From the Medical Clinic, Lakeside Hospital, the Laboratory of Hygiene and Bacteriology, and the Pharmacological Laboratory, Western Reserve University

1 It should be mentioned that the salted fish used for the preparation of the creamed fish for the patients had been inspected by the dietitian, as is her custom, and nothing unusual was found, either in appearance or in odor.

has not made a conspicuous inroad into clinical medical literature in the study of cases of ptomain poisoning. Those who are unfamiliar with the more recent aspects of the general subject of the physiologically active bases will find a clear and concise presentation of the subject in a recent monograph by Barger,<sup>2</sup> and in a work on toxicology by Gadamer.<sup>3</sup>

## I ONSET AND SYMPTOMS

BY M. A. BLANKENHORN

The following report is based on the personal observation of sixteen cases in one ward of the hospital. The remaining cases were distributed among other wards and the kitchens, and the reported observations on these differed in no respect from the account given here. In all, eighty individuals were seized with sudden and alarming symptoms of distress in the gastro-intestinal tract. Many of the patients volunteered the information that they were poisoned by the fish which was served with their meal, and it was evident that the symptoms were confined to those who had eaten the "creamed" fish, and that none who had eaten it escaped. The relief of so large a number of patients demanded so great and rapid attention that detailed observations in many of the cases could not be made. However, a sufficiently large number was studied to justify the following descriptive summary.

The symptoms appeared in about one and a half to three hours after the food was taken. The most marked symptom was vomiting. This occurred in every case, usually being sudden and very severe, preceded by a "burning" in the epigastrium, and much nausea, and accompanied by exhaustion, varying from slight discomfort to a semi-coma, lasting from two to five hours. The vomiting apparently bore no relation to the amount or quality of stomach content, for in some cases there was a large amount of macerated food ejected, and in others variable amounts of a clear, watery secretion. In many cases the vomiting persisted long after the stomach had been emptied. In all cases the vomitus was described as very sour and "burning." In several cases the acidity of the stomach contents was titrated with the following results: One hundred c c became neutral to phenolphthalein with 20 c c of tenth-normal sodium hydroxid; only a trace of free hydrochloric acid was present, and there was no lactic acid.

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<sup>2</sup> Barger. *The Simpler Natural Bases*. London, Longmans, Green & Co., 1914.

<sup>3</sup> Gadamer. *Lehrbuch der chemischen Toxikologie*, Göttingen, Vandenhoeck and Ruprecht, 1909.

Eleven out of sixteen patients vomited material which resembled blood, varying from just a visible trace of pink to dark red with masses resembling clots. No chemical tests for blood were made.

From one-half to two hours after the onset of vomiting there was intestinal colic and diarrhea, in some cases very slight, in others amounting to continuous purging for several hours. There were no evidences of fever, edema or skin disturbance.

Very little treatment could be instituted. Emetics and lavage with large quantities of water were administered to those who seemed to have difficulty in emptying the stomach. In a few cases castor oil or Epsom salt was introduced into the stomach after lavage.

All the patients were fairly comfortable at the end of from twelve to twenty-four hours, except for a feeling of exhaustion and a loss of appetite. Practically all had recovered by the next day. Very sick patients had not received the fish food, and there were apparently no lasting consequences in those who ate it.

## II BACTERIOLOGIC EXAMINATION

BY G. E. HARMON

The object of this examination was to ascertain if any organisms could be isolated from the "creamed" codfish which might have been concerned in forming toxins or poisons responsible for the symptoms observed in the patients. The usual routine procedures were used. The material was plated and grown anaerobically and aerobically.

No strictly anaerobic organisms were isolated. Those which were isolated by anaerobic methods could be grown in the presence of oxygen.

Numerous varieties of cocci were isolated. In view of the fact that cocci are thought not to be actively concerned in the production of putrefactive changes, no attempt was made to identify them definitely. Most of them were varieties of staphylococcus.

Four different kinds of bacilli were found and studied. Three of these were not identified, since a preliminary study of their characteristics showed them to be saprophytes, which did not produce gas in dextrose. This would exclude *Bacillus coli communis*. Presumably no other organisms were connected with the production of substances which would explain the symptoms in the cases reported. The fourth bacillus had the following characteristics. It was motile, gelatin was not liquefied, it was negative to Gram's stain, gas was produced in lactose, dextrose and saccharose broth, and litmus milk was acidified and coagulated. These characteristics serve to identify this organism as the *Bacillus coli communior*. No other important organisms were found.

## III PHYSIOLOGICAL AND CHEMICAL OBSERVATIONS

BY P J HANZLIK

Some of the "creamed" codfish as served to the patients was procured from the hospital dietitian<sup>4</sup> and various extracts made from it. These were then utilized in the physiologic and chemical observations to be described. These observations were controlled with extracts made from codfish (fresh and putrefied), salted codfish (fresh and putrefied) and both these varieties "creamed" and prepared in exactly the same way as the "creamed" fish which was served to the patients.

The "creamed" fish is prepared in the hospital as follows. The salted fish are macerated in water for twelve hours. The watery extract is then discarded and the fish is steamed. Then it is removed from the steamer and creamed with a mixture consisting of flour, butter and milk, and served in about one hour. In the meantime the prepared material is kept lukewarm within the steamer.

The preparation of the extracts of the "creamed" fish from the hospital, and the physiologic effects of these will be described first. Then the results of the control material will be presented, and finally, the chemical observations.

## 1 PREPARATION OF EXTRACTS

The extracts of the "creamed" fish were prepared as follows, using in each case 100 gm of the material, so that 1 cc of the finished product represented 1 gm of the material.

A The material was minced and macerated with distilled water and slightly acidified with hydrochloric acid. This was allowed to stand over night, then filtered and the filtrate made up to 100 cc. The excess of acid in the finished extract was removed by the addition of sodium hydroxid, leaving a slightly acid reaction to litmus as it was feared that important constituents might be lost by precipitation.

B The minced material was made moderately acid with hydrochloric acid and boiled with distilled water for two hours. Then it was filtered and the filtrate was made up to 100 cc. The excess of acid was again removed, leaving the finished extract slightly acid to litmus.

C The minced material was extracted with 98 per cent alcohol over night. Then the extract was filtered and the filtrate made up to 100 cc. Before using, the alcohol was removed by evaporation on the water bath and the residue was dissolved in water.

These extracts were now used in the physiologic observations to follow.

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<sup>4</sup> Thanks are due to Miss Graves, chief dietitian at Lakeside Hospital, for her kind cooperation in this investigation and to Mr. Betbower, supply agent, who secured the material. Inasmuch as the dietitian discovered no apparent putrefaction in the fish when it was used, it is probable that the spoiling must have occurred before the fish was salted and that the evidences of putrefaction were masked by the salting.



2 PHYSIOLOGIC EFFECTS

*Surviving Intestine*—Longitudinal and circular strips of cat's and rabbit's intestine were suspended in oxygenated Tyrode's solution, and their spontaneous movements were recorded on a slow moving drum by a weighted lever in the usual manner. The results obtained are briefly summarized in Table 1. Figures 1 and 2 will serve to illustrate some of the typical effects obtained.

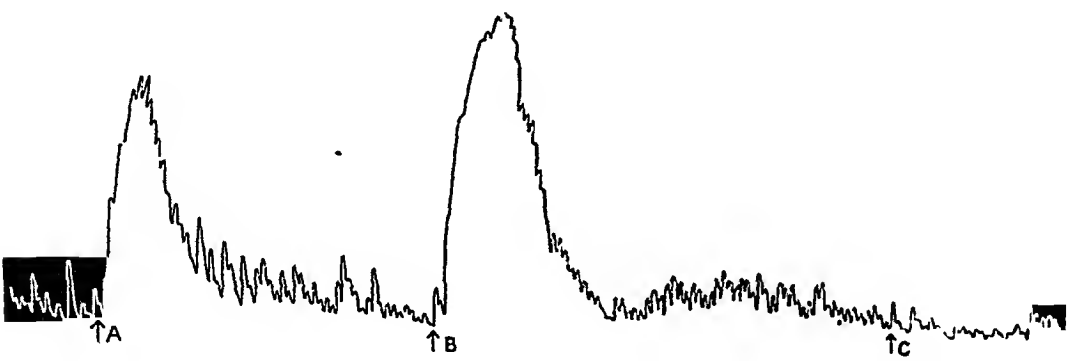


Fig 1—Effect of extracts of “creamed” fish (hospital material) on longitudinal strip of surviving cat's intestine. Tyrode solution at 37.5 C. A, 1 cc of Extract A (alkaline), B, 1 cc of Extract A (slightly acid), C, 2 cc of Extract B.

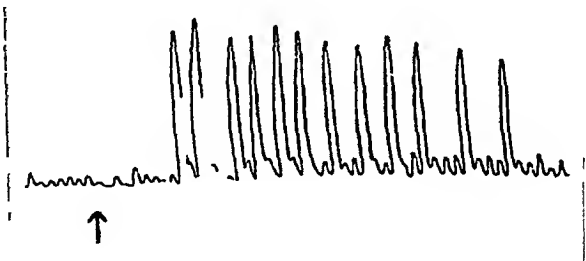


Fig 2—Effect of alcoholic extract of “creamed” fish (hospital material) on longitudinal strip of surviving cat's intestine. At point marked by arrow, 1 cc of Extract C.

TABLE 1—EFFECTS OF EXTRACTS OF “CREAMED” FISH ON SURVIVING INTESTINE

Extract *	Description of Peristalsis
A	Marked increase in tone, rate and amplitude only in some cases moderately increased. Same effects observed when extract was made alkaline.
B	No increase in tone, rate or amplitude.
C	Very slight increase in tone, in some cases marked increase in amplitude, rate unchanged.

\* One cc of the extract was usually added directly to the organ in 100 cc of Tyrode.

These show a stimulation of peristalsis with marked increase in tone and some increases in amplitude and rate, with the aqueous acid extract (A) of the "creamed" fish. The effects are not due to the acid reaction, as they took place equally readily when the extract was made alkaline or neutralized. The aqueous acid extract made by heat had no effect. The alcohol extract produced only an increase in the

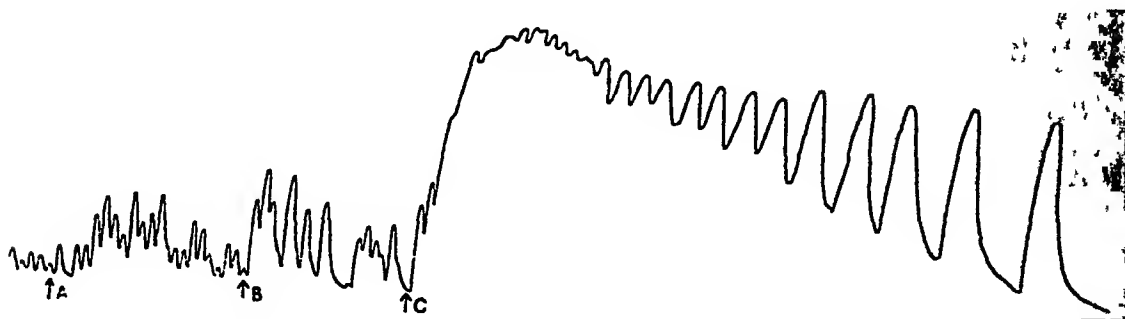


Fig 3—Effects of extracts of "creamed" putrefied codfish and "creamed" putrefied salted codfish (controls) on longitudinal strip of surviving cat's intestine. A, 2 cc of Extract I, B, 2 cc of Extract I, C, 2 cc of Extract J (creamed putrefied salted codfish)

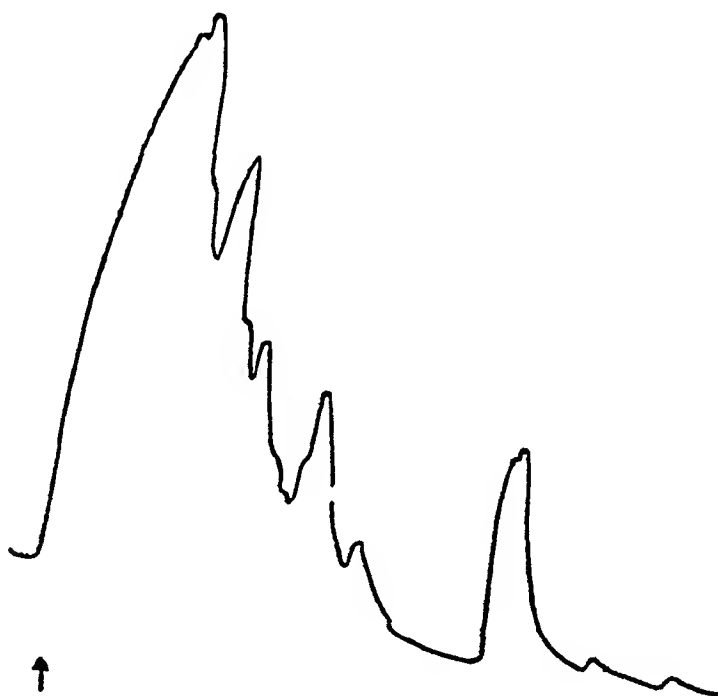


Fig 4—Effect of extract of "creamed" putrefied salted codfish (control) on strip of surviving pregnant uterus of guinea-pig. No spontaneous contractions for an hour before extract was applied. Arrow, 1 cc of Extract J

amplitude of peristalsis. The augmentor effects produced by the aqueous acid extract closely resemble those of histamin. Putrescin and cadaverin are said to produce analogous effects, though not so pronounced.

When it was ascertained that only the aqueous acid extract made in the cold gave the most constant and maximal effects, the extracts of the control material were made in this way. The control experiments were made in order to ascertain if physiologically active extracts required putrefied material, and whether or not the process used in the preparation of the "creamed" fish gave the optimal conditions. It was found to be true that only salted codfish when first allowed to putrefy and then was "creamed" and prepared according to the hospital method gave the most constant and typical physiologic effects. The results of these experiments are briefly summarized in Table 2,

TABLE 2—EFFECTS OF EXTRACTS OF FRESH, "CREAMED" FISH, PUTREFIED AND CREAMED PUTREFIED CODFISH AND SALTED CODFISH ON SURVIVING INTESTINE

Designation of Extract	Description of Extract *	Description of Peristalsis
D	Fresh codfish	No effect after several applications of 2 cc
E	Fresh salted codfish	No effect after several applications of 2 cc
F	"Creamed" fresh codfish	No effect after several applications of 2 cc
G	"Creamed" fresh salted codfish	No effect after several applications of 2 cc
H	Putrefied codfish	Very slight increase in amplitude and tone, diminution in rate with single applications of 2 cc
I	"Creamed" putrefied codfish	Very slight increase in tone and amplitude, somewhat more in rate after single applications of 2 cc
J	"Creamed" putrefied salted codfish	Very marked increase in tone which was lasting, marked increase in amplitude during relaxation, rate unchanged generally

\* One cc of each extract represents 1 gm of the material, which was macerated with distilled water and sufficient hydrochloric acid to give a moderately strong acid reaction. Before the extracts were used, the excess of acid was neutralized with sodium hydroxid, leaving a faint trace of acidity to litmus. Usually 2 cc of the extracts were used.

Figures 3 and 4 will illustrate the typical effects obtained, and Figure 5 the effects of epinephrin, atropin and papaverin on intestine treated with the active extract.

The results indicate that only the aqueous acid extract of the "creamed" putrefied salted codfish gave typical effects, and that these were practically identical with the effects obtained with the hospital material. Extracts from plain and "creamed" fresh or putrefied codfish and "creamed" fresh salted fish produced practically no effects. It is clear that putrefaction of the fish is essential for the production

of the augmentor effects on peristalsis. It seems also to be necessary to "cream" and prepare the fish as was done for the patients. This mode of preparation may establish some suitable condition under which liberation of the active chemical substances takes place. It will be shown later that apparently a certain bacterial environment is also necessary to produce physiologically active culture mediums.

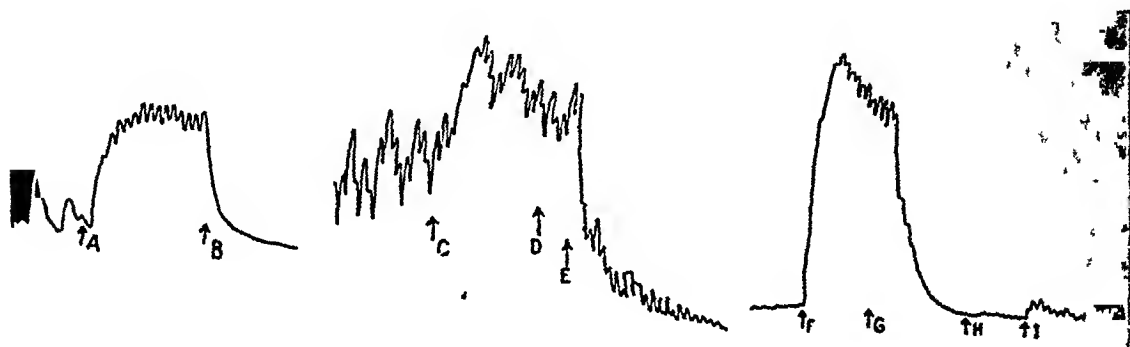


Fig 5—Effects of epinephrin, atropin and papaverin on surviving cat's intestine treated with extract of "creamed" putrefied salted codfish. A, 1 cc of Extract J, B, 0.2 cc of epinephrin, 1:1,000, C, 1 cc of Extract J, D, 0.2 cc of papaverin hydrochlorid, 1:1,000, E, 0.2 cc of papaverin hydrochlorid, 1:1,000, F, 1 cc of Extract J, G, 0.1 cc of atropin sulphate, 1 per cent, H, 1 cc of Extract J, I, 1 cc of Extract J.

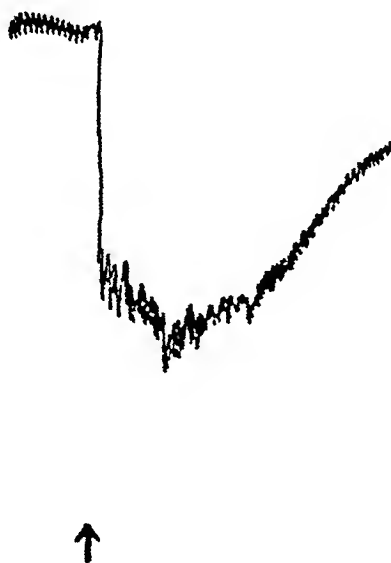


Fig 6—Effect of acid extract of "creamed" putrefied salted codfish on systemic blood pressure (dog, 5.6 kg). At arrow, 1 cc of Extract J per kilogram intravenously.

*Surviving Uterus*—The effects produced were essentially similar to those on the intestine, namely, a marked stimulation of peristalsis. Figure 4 illustrates a typical reaction with the aqueous acid extract of putrefied "creamed" codfish.

*Blood Pressure*—The various extracts were injected intravenously into dogs, and the blood pressure was recorded by a dampened mercury

manometer in the usual manner. The dosage varied from 1 to 2 cc per kilogram. All of the extracts from the hospital material and the controls produced a fall in blood pressure followed by a rise, except the aqueous acid extract (A) of "creamed" putrefied salted codfish, in which the fall was not followed by a rise in pressure, but rather a slow tendency to recovery. This result was constant, and resembles the characteristic effects obtained with histamin. The initial rapid fall is presumably of endocardial origin. A pressor effect in the same animal was obtained after the injection of epinephrin, showing that the mechanism by which this is brought about was functionally active. The fall in pressure could not be due to albumoses or peptone because some of the other extracts which contained these substances did not give the typical effect of Extract A. On the contrary, a slight rise in pressure was usually obtained after the primary fall. Figure 6 illustrates a typical blood-pressure effect.

### 3 EFFECT OF BACTERIAL CULTURES OF "CREAMED" FISH ON SURVIVING INTESTINE

The various culture mediums which were incubated with the hospital material by Dr. Harmon were applied directly to strips of surviving intestine. The object of this was to ascertain roughly, if possible, the kind of environment (as judged by mediums of different

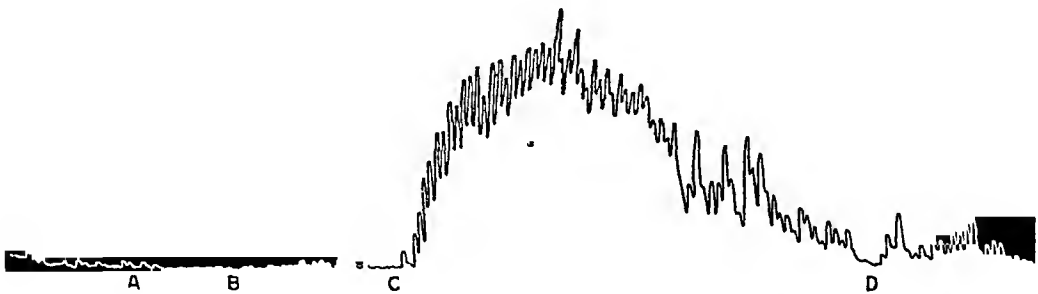


Fig. 7—Effects of culture mediums incubated with "creamed" fish on surviving cat's intestine. A, 2 cc of bouillon culture of fish food, B, 2 cc of lacmus milk culture of fish food, C, 2 cc of bouillon dextrose culture of fish food, D, 0.5 cc of 10 per cent sugar.

composition) that is most favorable to the organisms for the development of the physiologically active toxic substances. It was interesting to find that only one culture, namely, bouillon-dextrose, out of several that were used, produced a physiologic response, and this resembles essentially the effects produced by the aqueous extract (A) of the hospital material itself. The effects of plain bouillon and dextrose

alone were excluded because no effects were produced by the inoculated mediums. The effects of the various cultures are briefly summarized in Table 3 and illustrated by Figure 7.

TABLE 3—EFFECTS OF CULTURES INCUBATED WITH “CREAMED” FISH ON SURVIVING INTESTINE

Culture Medium and Quantity Used	Description of Peristalsis
Plain bouillon, 2 cc	No effect on tone, rate or amplitude
Lacmus milk, 2 cc	No effect on tone, rate or amplitude
Emulsion from agar stab, 2 cc	No effect on tone, rate or amplitude
Bouillon-dextrose, 2 cc	Marked increase in tone, some increase in rate, no increase in amplitude
Dextrose 10%, 2 cc	No effect on peristalsis
Extract A (fish)	Marked increase in tone, some increase in rate and amplitude. Effect removed by 0.2 cc papaverin HCl 0.1 per cent.

#### 4. CHEMICAL OBSERVATIONS

The general principles recommended in Barger's monograph for the extraction and purification of the simpler bases were followed. As no more of the hospital material was available, the “creamed” putrefied salted codfish used in the control experiments, which behaved similarly physiologically, was used. No attempt was made to isolate the active chemical substance or substances in the form of pure salts as the technic is beset with numerous difficulties and would require more time than was justified in spending. As pure an extract was obtained as possible which would permit the application of certain of the group reactions for the supposed bases and other products.

An aqueous acid extract in the cold of the “creamed” putrefied salted codfish was made by treating about 200 gm of the macerated material with hydrochloric acid. The material was thoroughly expressed and the liquid extract evaporated and dried in vacuum. It was necessary to eliminate the use of heat, since it was found that an extract obtained by heat was physiologically inactive, and it is known that many of the bases are destroyed by heat. The thick smeary residue was then treated with 95 per cent alcohol to remove as much protein and other precipitable materials as possible. Enough water was present under these conditions to retain the active bases in solution. The alcohol was removed by spontaneous evaporation at first, and finally, in vacuum. The residue now remaining was treated with water, and appeared to dissolve completely with some opacity. This was then treated with both the basic and ordinary lead

acetate three times, the lead being removed each time by precipitation with hydrogen sulphid. Finally, when all the lead was removed, the remaining extract, which appeared to have a slightly yellowish tint, was treated with animal charcoal in the cold and filtered. The filtrate appeared entirely colorless and transparent. This filtrate was then used for the various tests as follows:

1 Pauly's reaction<sup>5</sup> with p-diazobenzene sulphonate gave a yellowish with rose-pink at first and finally a deep orange. This was controlled with a very dilute solution of histamin, which gave a similar set of colors, namely, yellow with rose-pink at first and finally a deep orange. A strong histamin solution gave colors which were more intense. The reagent alone gave a very light yellow which did not develop as rapidly as with the filtrate or histamin, and showed no rose-pink or deep orange. Dialyzed egg-albumin gave the same as the reagent alone, but a weak peptone solution gave colors very similar to those of the extract and histamin.

2 The fish extract did not give a positive biuret test. This would exclude protein, such products as peptone and also histidin.

3 Knoop's test (boiling with bromin water) was not positive. This would also exclude histidin.

The results obtained with these tests roughly indicate that the general group of diamins is concerned. To this group belong histamin, putrescin and cadaverin. It is not maintained that the presence of either one or all of these products is demonstrated. However, other substances which are said to give Pauly's reaction, such as alcohol, chrysarobin, creosote, cresols, dionin, guaiacol, heroin, morphin, naphthol, opium, phenol, tannic acid, etc.,<sup>6</sup> do not come into consideration here, purins and other analogous products which occur in normal urine (also positive with Pauly's reagent, though not characteristically), and also tyramin, are excluded because these do not give any known physiologic reactions such as were obtained with extracts of the fish material, or clinical symptoms as exhibited by the patients.

#### IV COMMENT

BY P. J. HANZLIK

From the nature of the clinical evidence obtained, it appears that the symptomatic attack which seized the patients was not of bacterial origin. The attacks took place within three hours, which is much,

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5 The reagents used in this reaction are (1) 0.5 per cent solution of sodium nitrite, and (2) 0.5 per cent solution of sodium sulphanilate. The reagents are used in the proportion of 1 of the nitrite to 50 of the sulphanilate and are not mixed until the test is to be made.

6 Hawk. Practical Physiological Chemistry, Philadelphia, P. Blakiston's Son & Co., 1913, p. 360.

shorter than the incubation period of any known organism. It appears, then, that some other cause was present. This might be chemical, that is, some chemical substance, which was already present in the fish food before it was ingested. The origin of this, in turn, might be bacterial or autolytic. It is presumed that it was bacterial. The rapidity, violence and suddenness of the attacks would indicate some active chemical substance which was preformed and readily absorbed.

Physiologically, it can be said that the experiments on surviving organs indicate that some substance markedly stimulating to peristalsis was present in the material. The tone of both intestinal and uterine musculature was markedly increased. In fact, this seemed to be the most striking effect. However, the rate and amplitude of the intestinal peristalsis were also increased at times. These reactions would not necessarily explain the gastro-intestinal symptoms observed in the patients, but it is suggestive. Increased peristalsis of the intact intestine was observed in a dog which had received an intravenous injection of the most active fish extract (A). These effects are quite analogous to those obtained with histamin and similar diamins, such as putrescin and cadaverin, which can be prepared from decomposed flesh. The effect on the systemic blood pressure resembled that of histamin, namely, a fall with a gradual tendency to recovery. These reactions cannot be attributed to protein or its decomposition products, such as albumoses and peptones, or even purins, because many of these are not known to have any such physiologic effects, and moreover, certain of the extracts which contained these products produced no effects. It would appear that these physiologic actions are due to some chemical substance which is elaborated under certain favorable conditions, namely, from salted codfish which is previously allowed to putrefy and then is "creamed" and prepared as described in the text. An aqueous acid (hydrochloric acid) extract of such fish food gave the most marked and constant typical effects. A similar extraction could conceivably occur in the stomach, that is, by the solvent and digestive power of the gastric juice. The alkalinity of the intestine would not remove the physiologic effects, as no interference with the typical intestinal reaction was observed when the active acid extract was rendered alkaline.

The chemical evidence is incomplete. However, it may be stated that the physiologically active substance is destroyed by prolonged boiling, as the boiled extracts were inactive. Alcohol does not remove it completely. An aqueous acid (hydrochloric acid) extract in the cold was the most active and gave constant results. (Only the "creamed" putrefied salted codfish is here referred to, as the fresh fish and salt fish under other conditions gave inactive extracts.) The



fact that Pauly's reaction with p-diazobenzene sulphonate was positive in the absence of protein (excluded by purification and negative biuret reaction) seems to indicate that some base belonging to the general group of diamins represented by such products as histamin, putrescin and cadaverin derived from putrefied flesh is present. The presence of putrins and other analogous substances is excluded by the nature of the symptoms and the physiologic effects on blood pressure and surviving organs.

## V CONCLUSIONS

1 The clinical symptoms observed in a large number of patients attacked with ptomain poisoning from "creamed" salted codfish were epigastric distress, nausea, vomiting, intestinal colic and diarrhea. Complete recovery occurred in from twelve to twenty-four hours, in a part of the individuals spontaneously, and in another part following gastric lavage.

2 Bacteriologic examination of the "creamed" fish showed the presence of the *Bacillus coli communior*, and other saprophytes and some staphylococci.

3 The gastro-intestinal disturbances are not attributed to infection by the organisms in the fish material.

4 Extracts of the "creamed" fish gave practically the same physiologic reactions as the same brand of salted codfish which was previously allowed to putrefy and then was prepared in the same manner as the food served to the patients.

5 The physiologic effects consisted of a marked stimulation of intestinal and uterine peristalsis with surviving organs, and a fall of blood pressure with gradual recovery.

6 The purified active extract of the "creamed" putrefied salted codfish contained some physiologically active base, whose chemical reactions resemble those of the group of diamins to which putrescin, cadaverin and histamin belong.

# OBSERVATIONS ON SINO-AURICULAR HEART BLOCK <sup>1</sup>

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Heart block is ordinarily understood to be a condition in which there is impairment in the conduction of impulses from auricles to ventricles. The first stage of this process is represented by a mere delay in the conduction time recognized by an increase in the a-c interval in jugular tracings and in the P-R time in electrocardiograms. In this condition all impulses reach the ventricle, but if the delay is sufficient or if the heart rate is rapid, an impulse may occasionally fail to reach the ventricle, giving partial heart block. Finally, there is a condition in which none of the auricular impulses reach the ventricle, and the auricles and ventricles each beat of their own rhythm and independently of one another. These three stages may be termed, first, *delayed conduction*, second, *partial heart block*, and third, *complete heart block*. The cause of this disturbance in heart mechanism lies in the effect of some toxin or some degenerative change on the auriculo-ventricular node of Tawara or on the main stem of the bundle of His. Any of the three stages may result from the action of digitalis, from acute febrile conditions, particularly rheumatic fever, and from chronic degenerative processes involving the conductive mechanism of the heart, such as cardiac sclerosis or gummas.

It might be expected that changes similar to those which occur in the auriculo-ventricular node and bundle of His would take place when similar abnormal conditions existed in the vicinity of the sino-auricular node, which has much the same function and structure as the auriculo-ventricular node. One is, in fact, surprised that defective conduction between the sinus node and auricle is so rarely observed. As at present there is no simple means of determining a sino-auricular (S-A) interval corresponding to the auriculoventricular interval (a-c or P-R), delayed conduction in this region, if it occurs, cannot be recognized. It follows that not all conditions in which the first stage of block might exist are recognized as such, for the S-A interval may be much prolonged without causing any change detectable by any of the graphic methods of heart diagnosis. However, if the second stage of block is

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<sup>1</sup> This work was done under a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases in the Medical Clinic of the Peter Bent Brigham Hospital

present, then the condition can be recognized either by jugular tracings or more accurately by electrocardiograms, for a complete heart cycle is dropped and the pause is approximately twice the length of the normal heart cycle. Four such cases observed by the author in the medical clinic of the Peter Bent Brigham Hospital are here reported with a historical review of the subject, and certain observations on the condition.

### HISTORICAL REVIEW

In 1883 Gaskell<sup>1</sup> showed that the *primum movens* in the tortoise's heart was located near the mouth of the great veins. Between that time and 1907, when Keith and Flack<sup>2</sup> made the discovery that histologically there could be seen a specialized tissue in this vicinity, many investigators have published results similar to Gaskell's, working with various cold and warm blooded animals. It has long been known that the automaticity and the rhythmicity of the heart musculature diminishes from above downward, that is, under normal conditions the sinus region is most automatic, and in lesser degree the auricles and ventricles, respectively. This explains to some extent why the cardiac impulse and contraction first appears in the region of the great vessels and spreads downward. It has always been a debatable question, however, whether the activity in the sinus region produces any noticeable effect either in animals or in the human being. Is there a real sinus wave in the normal jugular curve due to the contraction of the superior vena cava? Hering<sup>3</sup> in 1900, experimenting on dogs and rabbits, brought out the contraction of the big veins by cooling the sinus region thereby slowing the rate of the heart. He said

The slower the heart action now becomes, the more plainly one may see that unquestionably the pulsation of the veins precede that of the auricles. Furthermore, one can see that only after several pulsations of the vein does an auricular contraction follow. Finally, the veins pulsate very feebly without being followed by any auricular contraction.<sup>4</sup>

Erlanger,<sup>5</sup> in his exhaustive study of heart block, suggests that a positive wave in the neck before the auricular systole, in a case which

1 Gaskell, W. H. On the Innervation of the Heart, with Especial Reference to the Heart of the Tortoise, Jour. Physiol., 1883, iv, 43.

2 Keith, A., and Flack, M. The Form and Nature of the Muscular Connections Between the Primary Divisions of the Vertebrate Heart, Jour. Anat. and Physiol., 1907, xli, 172.

3 Hering, H. E. Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages, Arch. f. d. ges. Physiol., 1900, lxxxii, 1.

4 Je langsamer nun die Herzaction wird desto deutlicher sieht man dass ganz unzweifelhaft den Pulsationen der Venen, jene der Vorhöfe folgen. Weiterhin kann man beobachten dass erst auf mehrere Pulsationen der Vene eine Vorhofscontraction folgt. Schliesslich pulsieren nur noch die Venen ganz schwach, ohne von Vorhofschlägen gefolgt zu werden.

5 Erlanger, J. On the Physiology of Heart Block in Mammals, with Especial Reference to the Causation of Stokes-Adams' Disease, Jour. Exper. Med., 1905, vii, 676.

had complete heart block and which therefore permitted the auricular waves to appear distinctly during the long ventricular pauses, may be due to the contraction of the great veins. The curves of this case are quite clear, but there is a considerable interval between these sinus waves and the auricular waves, which is contrary to the work recently reported by Eyster and Meek<sup>6</sup>. These authors have shown that the impulse travels from the pace maker at the head of the sinus node upward to the superior vena cava quite rapidly, and to the auricular musculature more slowly, but the difference in speed is not greater than 0.02 second. Considering that conduction is less rapid in the human heart, it is still much too short a time to permit any distinct wave to appear.

It may well be that a sinus wave appears distinctly in the jugular curves only under the most favorable circumstances. The proper venous pressure may be necessary. Or if there is a delay in the conduction of the impulse from sinus region to the auricles, a small wave due to the contraction of the mouth of the superior vena cava might appear which otherwise would have been lost in the auricular wave. These several factors may account for the failure in most instances to obtain such a wave either in animals or in man. The same uncertainty exists in electrocardiography. It is thought by some investigators that a split "P" wave does not necessarily represent the retarded contraction of one or the other auricle, but that it is due to sinus activity. Hering,<sup>7</sup> by vagal stimulation in dogs, caused a small wave to appear 0.02 second before the "P" wave in electrocardiograms. Von Hoesslin<sup>8</sup> found that the "P" waves became notched during vagal pressure in man, but that the notch came after the point where the auricular complex started, that is, between the P and R waves. One must distinguish in this connection between a possible pressure wave as a result of the contraction of the superior vena cava and a wave in the electrocardiogram as a result of sinus activity. They have both been called sinus waves, but their causes and their time relations are different. The latter must necessarily come before the main auricular complex, while the occurrence of the former will depend on the relative speed with which the impulse reaches the veins and the auricles. Kahn<sup>9</sup> found a notch in the P wave of horses which would come 0.04 second after the beginning of the auricular complex, but in some cases the

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6 Eyster, J. A. E., and Meek, W. J. Experiments on the Origin and Propagation of the Impulse in the Heart, *Heart*, 1914, v, 119.

7 Hering, H. E. Experimentelle Studien an Säugethieren über das Elektrokardiogramm, *Arch f d ges Physiol*, 1909, cxxvii, 155.

8 Von Hoesslin, H. Beobachtungen über den Einfluss des vagus auf das menschliche Herz, *Deutsch Arch f klin Med*, 1914, cxiii, 537.

9 Kahn, R. H. Das Pferde-Ekg, *Arch f d ges physiol*, 1913, cliv, 1.

second portion of the curve would be smaller than the first. On measuring back from the first point of the mechanical curves traced by the auricular contraction, and assuming that the time from the electrical to the mechanical evidence of contraction is the same for auricle and ventricle, he found that the first part of the wave corresponded to auricular contraction. It is difficult, therefore, to explain a notching which occurs after the auricular complex has begun, as due to activity in the pace maker which is first to become electrically negative. Weil,<sup>10</sup> in a recent publication, states that the notching of the P wave is due to delayed conduction in the sinus node, or between the node and the auricles and that the first part is a result of sinus activity. According to Norr,<sup>11</sup> in the electrocardiogram of some horses a distinct wave is seen 0.08 second before the auricular wave, which he thought was due to the contraction of the great veins. One can readily see from this brief résumé that the question of sinus waves is unsettled and problematic.

It is not necessary that there should be an evident wave in the electrocardiogram as a result of sinus activity in order to draw conclusions as to physiologic and pathologic processes going on in the S-A node. It has been shown by Lewis, Oppenheimer and Oppenheimer<sup>12</sup> that over the specialized tissue described by Keith and Flack there is a point on the sulcus terminalis and in the immediate neighborhood of its upper extremity, close to the cavo-auricular angle, which becomes electrically negative before any other part of the auricular musculature. Eyster and Meek,<sup>6</sup> using the same index, determined the course of the impulse in the mammalian heart by placing two electrodes on various portions of the auricles. They found that the impulse started at the upper end of the node and traveled most rapidly to the mouth of the superior vena cava and less rapidly to the lower part of the node itself. According to their calculations, it took 0.01 second to reach the lower part of the node, but a shorter time was required to reach the superior vena cava, while to a point on the right auricle only 2 or 3 mm away from the node, the duration was from "0.015 to 0.025" second.

Blocking of impulses at the pace maker was observed experimentally by Hering<sup>3</sup> in 1900, and later<sup>13</sup> in 1906 he obtained pauses of the auricles and ventricles approximately twice the normal length by

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10 Weil, A. Beiträge zur klinischen Elektrokardiographie, *Deutsch Arch f klin Med*, 1914, cxvi, 486.

11 Norr, J. Das Elektrokardiogramm des Pferdes. Seine Aufnahme und Form, *Ztschr f Biol*, 1913, lxi, 197.

12 Lewis, T., Oppenheimer, B. S., and Oppenheimer, A. The Site of Origin of the Mammalian Heart Beat, *Heart*, 1910-1911, ii, 147.

13 Hering, H. E. Ueberleitungsstörungen am Säugethierherzen mit zeitweiligen Vorhofsystolenausfall, *Ztschr f exper Path u Therap*, 1906, iii, 511.

clamping the A-V node Erlanger and Blackman<sup>14</sup> were able to make the veins of the rabbit beat twice as fast as the auricles by passing a thread down the superior vena cava and out through the inferior cava and twisting the thread, the torsion causing pressure on the S-A node In a later publication, Erlanger<sup>15</sup> thought that in similar experiments when the auricles were beating regularly and slowly there was complete sino-auricular dissociation In studying the effect of aconite on dogs, Cushny<sup>16</sup> noticed sudden halvings of the auricular and ventricular rate, which he thought was due to a blocking of every other impulse at the sinus node

#### REVIEW OF CLINICAL CASES OF SINO-AURICULAR BLOCK

From a clinical standpoint, occasional cases showing sino-auricular block have been reported In 1902 Mackenzie<sup>17</sup> discussed a case and showed radial and jugular tracings in which there were pauses approximately twice the normal heart cycle During some of these pauses an "a" wave appeared in the jugular, while during others no wave was present He did not say that the failure of the auricles to contract was due to a S-A block, but it seems quite possible from his tracings that there was block present in both nodes Joachim<sup>18</sup> reported four cases of heart block with radial tracings of two and both radial and jugular tracings of the other two The pauses in the radial tracings were more or less short of being twice the length of the normal cycle The "a" waves were absent in the jugular curves during the pauses In three of these cases the cycle after the pause was generally longer than the other normal cycles (Reference to this point will be made later in connection with the cases observed by the author)

Wenckebach<sup>19</sup> discussed two cases of heart block showing jugular and radial tracings The first one was a young man in good health who showed a gradual increase in the a-c interval until an "a" wave appeared in the neck which was not followed by a ventricular beat Following this pause, however, neither auricle nor ventricle contracted, which signified that the impulse was blocked at the S-A node The

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14 Erlanger, J, and Blackman, J R A Study of Relative Rhythmicity and Conductivity in Various Regions of the Auricles of the Mammalian Heart, *Am Jour Physiol*, 1907, xix, 125

15 Erlanger, J Irregularities of the Heart Resulting from Disturbed Conductivity, *Am Jour Med Sc*, 1908, cxxxv, 797

16 Cushny, A R The Irregularities of the Mammalian Heart Observed under Aconite and on Electrical Stimulation, *Heart*, 1909, i, 1

17 Mackenzie, J The Cause of Heart Irregularities in Influenza, *Brit Med Jour*, 1902, ii, 1411

18 Joachim, G Vier Falle von Störung des Reizleitung im Herzmuskel, *Deutsch Arch f klin Med*, 1905, lxxxv, 373

19 Wenckebach, K F Beiträge zur Kenntnis der Menschlichen Herz-tätigkeit, *Arch f Anat u Physiol, Physiol Abt*, 1906, p 297

second case was one of hypertension with an intermittent pulse, the pauses being twice the normal heart cycles. The a-c interval was at no time increased, and in all but two occasions "a" waves appeared in the jugular. The failure of the auricles to contract on these two occasions he thought was due to insufficient irritability of the auricles. Hewlett,<sup>20</sup> in 1907, reported a case which showed ordinary a-v block with occasional instances in which the auricles as well as the ventricles were blocked. The pauses in the latter instances were almost equal to two heart cycles. There was also present a slight sinus arrhythmia.

In the case reported by Gibson<sup>21</sup> the patient had a history of syphilis, acute rheumatic fever and excessive use of alcohol, hypertension was present. Polygraphic tracings showed that the a-c interval was 0.7 second and that every other ventricular beat was blocked. A small wave which appeared 0.7 second before the "a" wave was thought to be due to contraction of the superior vena cava. This very long S-A interval must be accepted with some doubt, although it did diminish to 0.4 second eleven minutes after an atropin injection.

Rühl<sup>22</sup> reported a rather doubtful case with radial and jugular tracings in which there were pauses a little less than twice the length of one heart cycle, some having "a" waves and others not. The patient had been on digitalis at the time. A very striking instance of prolonged arrest of all chambers of the heart was reported by Laslett<sup>23</sup> in which the patient had attacks of faintness during the long pauses. The periods of inhibition do not measure out to be multiples of the normal heart cycle, and so it is questionable whether impulses were really blocked or whether it was a vagus slowing of the pace maker itself. The fact that excitement and exertion made these pauses disappear is in favor of the latter. In a more recent contribution by Riebold,<sup>24</sup> although no tracings were given, numerous interesting figures of the heart rate appeared. A young man quite sick with typhoid had a pulse rate of 120. A few days later the pulse was coupled at the rate of 80, and then it became regular at the rate of 40. At other times it was noticed to be regular with a rate of 60. Digitalis had been given, and because these figures are all simple fractions of the original

20 Hewlett, A. W. Digitalis Heart Block, Jour Am Med Assn, 1907, XLVIII, 47.

21 Gibson, G. A. Further Observations on Heart Block, Practitioner, London, 1907, p. 589.

22 Rühl, J. Klinischer Beitrag zur Kenntnis der Ueberleitungsstörungen von der Bildungsstätte der Ursprungsreize zum Vorhof, Deutsch Arch f klin Med, 1908, CIV, 286.

23 Laslett, E. E. Syncopal Attacks Associated with Prolonged Arrest of the Whole Heart, Quart Jour Med, 1908-1909, II, 347.

24 Riebold, G. Reizleitungsstörungen zwischen der Bildungsstätte der Ursprungsreize der Herzkontraktrone in Sinus der Oberen Hohlvene und dem Vorhof (sino-auricularer Herzblock), Ztschr f klin Med, 1911, LXXIII, 1.

pulse rate 120, it was thought that at first all sinus beats came through and later every third, then every second, or two of every three beats were blocked at the S-A node. It is surprising to note, if this be true, that the sinus rate remained constantly at 120 during the entire time. There was given no reliable evidence that the block did not take place at the a-c node. In the second case reported by the same author, after a third injection of 1 drop of tincture of strophanthus, the pulse fell from 102 to 51, and during the next few days was counted at 34, 25, 20 and 17, namely, one-half, one-third, one-fourth, one-fifth and one-sixth of the original rate of 102. It is fair to say that during such long pauses it ought to be less difficult than usual to hear the auricular contractions, and to see the auricular waves in the jugular vein. No such signs were made out here. It was therefore concluded that varying degrees of block were present at the S-A node.

An electrocardiographic study of a case of acute rheumatic fever by Schott<sup>25</sup> describes a condition of paroxysmal tachycardia with a regular rate of 200 coming after the patient had been fever-free for two weeks. During the tachycardia there were pauses exactly equal to two or three heart cycles, in which no waves were present at all.

In Table 1 are collected summaries of the fourteen cases of S-A block<sup>26</sup> which could be found in the literature, together with the four cases reported here. Only one of the cases from the literature was studied with the electrocardiograph, two were studied with radial tracings, two without any of the graphic methods, and all the rest with simultaneous jugular and radial tracings. Of these eighteen cases, ten manifested the arrhythmia only after having been given digitalis or some related body such as strophanthin, in four cases digitalis was definitely in no way related to the arrhythmia, in two nothing is said about digitalis, and in the last two, although no statement is made, the patients were suffering from cardiac decompensation and so might well have received it. Of the four cases that were not related to digitalis, one had S-A block during attacks of paroxysmal tachycardia which occurred during the convalescence from acute rheumatic fever, another was in a man who was otherwise well, the third was in a woman who had chronic cardiac trouble with attacks of syncope, and the fourth is Case 1 described below. The third case is better classified as one of vagal inhibition rather than S-A block, for the condition was not persistent and the pauses were not sufficiently approximate to

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25 Schott, E. Ueber Vorhofsystolenausfall, *Munchen med Wchnschr*, 1912, lix, 292.

26 Since this paper was written one case of sino-auricular block in a healthy man was described by J. A. E. Eyster and J. S. Evans, *THE ARCHIVES INT MED*, 1915, xvi, 832. Two other electrocardiograms of S-A block were noticed in T. Lewis' "Clinical Electrocardiography," one of which resulted from digitalis therapy.



simple multiples of the length of the normal heart cycles (Laslett's case) Most of the cases showed a greater or lesser degree of sinus arrhythmia (see Table 1) The significance of this will be taken up more fully later

Of the four cases which were studied here, the first two will be taken up in greater detail because they may serve as two different types, while the last two will be just briefly mentioned because the condition was only the incidental result of digitalis therapy

CASE 1 (Medical No 1991) —K S, a short stout woman, aged 56, entered the hospital, Dec 3, 1914, complaining of a jumping heart The patient had never been sick before The family history was unimportant About one month before the patient was taken ill with a severe "cold" in the head and chest and had severe diarrhea, ten movements a day She noticed for the first time that her heart jumped This condition lasted one week The heart quieted down and then she was well for ten days A similar attack in which her cardiac symptom was more prominent and her gastro-intestinal less so began two weeks ago The diarrhea cleared up in a few days but the jumping of the heart persisted and this brought her to the hospital

On physical examination it was found that the eyes, ears and nose were normal, teeth were in poor condition, the skin showed some dermatographia, the lungs were hyperresonant The heart borders were very difficult to determine The left border was about 12.5 cm from the midline in the fifth interspace The sounds were irregular, that is, after every third or fourth beat there was a long pause, and the systolic murmur after the long pause was slightly accentuated During the pause no sound could be heard and no wave could be seen in the jugular vein Sino-auricular block was present The pulses were equal and showed the same arrhythmia as the heart sounds The arteries were somewhat rigid and under high tension Systolic blood pressure was 196 and diastolic 98 The abdomen and extremities were negative The deep reflexes were present but somewhat active The urine had a specific gravity of 1.028, there was a slight trace of albumin and no sugar One hyaline cast was seen in five examinations Phenolsulphonephthalein output in two hours was 41 per cent Blood nitrogen, 23 mg per hundred c c of blood Blood Wassermann was negative The condition of the patient remained about the same except that she gained strength so that in seventeen days she walked out of the hospital without any difficulty Numerous electrocardiograms were taken, some simultaneously with jugular and brachial curves

Feb 24, 1915, the patient returned to the outdoor department complaining of constipation and bleeding hemorrhoids At this time further electrocardiograms were taken which showed that her arrhythmia remained practically unchanged She did quite well under medical treatment, but on April 22, 1915, she was again admitted to the wards for further study Observations on the effect of atropin and vagal pressure were made During this period of five months many electrocardiograms were taken, and the same condition of S-A block was always present No digitalis was administered at any time In July, 1915, it was learned that the patient was up and about, and doing a moderate amount of housework

CASE 2 (Medical No 2212) —Man, aged 42, boiler-maker, entered the hospital Jan 23, 1915, suffering from shortness of breath and swelling of the feet His mother died of diabetes and heart trouble There was an asthmatic history in the father's family The patient had married twice, and both wives had many miscarriages He had used tobacco and alcohol to excess and had always done hard muscular work under poor hygienic conditions He had measles, diphtheria, scarlet fever, malaria, smallpox, pneumonia, gonorrhea, and three

TABLE 1—REVIEW OF CASES

Case	Diagnosis	Sex*	Age	Blood Pressure	A O Interval, Second	History of Rheumatic Fever	Trachings	Relation of Digitalis to Arrhythmia	Length of Consecutive Heart Cycles, Including the Blocked Beat, Second	Extreme Sinus Variations in Length of Heart Cycles, Second
MacKenzie	Influenza	♂	40	?	0.1	?	Jugular, radial	Not stated	0.94, 0.81, 0.84, 0.82, 1.70, 0.96, 1.72, 1.72, 0.94, 0.84	0.82 to 0.96
	1 Cardiac decompensation	♀	73	?	?	?	Radial	Not stated	0.56, 0.54, 0.54, 0.56, 0.54, 1.04, 0.60, 0.56	0.54 to 0.60
	2 Mitral insufficiency, neutropericarditis	♂	15	S, 92	?	+	Radial	Occurred after 6 days of digitalis, did not recur after withdrawal	0.60, 1.16, 1.20, 0.76, 0.60, 0.56	0.56 to 0.76
Wenckebach	3 Mitral stenosis, cardiac decompensation	♂	24	S, 95	0.4 to 0.7	+	Jugular, radial	First noticed 2 days after digitalis	0.70, 0.72, 1.36, 0.76, 0.74, 0.70, 1.76, 0.76, 0.66	0.66 to 0.76
	4 Aortic insufficiency, cardiac decompensation	♂	67	?	0.32	+	Jugular, radial	After 4 days of digitalis	1.58, 0.98, 1.58, 0.98	Cannot be determined
	1 No disease	♂	30	?	0.2 to 0.4	?	Jugular, radial	Not stated, but probably not given	0.78, 0.66, 0.68, 0.70, 1.18, 0.78, 0.66	0.66 to 0.78
Hewlett	2 Cardiac decompensation without valve lesions	?	?	++	0.2	?	Jugular, radial	Not stated, but might have been given	0.92, 1.86, 0.88, 0.82	0.76 to 1.00
	Chronic alcoholism, hepatic cirrhosis, arteriosclerosis	♂	44	?	0.25 to 0.4	—	Jugular, radial	Had digitalis for 10 days before arrhythmia was observed	1.04, 1.03, 1.85, 1.84, 1.09, 1.01	0.93 to 1.08
	Cardiac decompensation	♂	66	S, 190 D, 80	0.7	+	Jugular, radial	Not stated	No blocked sinus beats	Cannot be determined
Ruhl	Chronic endocarditis, decompensated	♀	63	S, 120	0.24	—	Jugular, radial	Had digitalis for 7 days before observed	0.66, 1.30, 0.70, 0.66, 1.42, 0.76	0.66 to 0.76
	Chronic myocarditis	♀	40	?	0.2	?	Jugular, radial	Not related to digitalis	1.20, 1.16, 4.20, 1.08, 1.12, 1.80, 1.08, 1.20, 1.10, 1.30	1.08 to 1.30
	1 Severe typhoid	♂	23	?	?	?	None	Digitalis was given before arrhythmia appeared	No sinus variation	
Schott	2 Arteriosclerosis, decompensation	♂	67	?	?	?	None	After 3 injections of straphanthus	0.35, 0.35, 1.05, 0.95	
	Acute rheumatic fever, paroxysmal tachycardia	♂	23	S, 120 D, 85	0.2	+	Electrocardiogram, jugular radial	No digitalis used	0.86, 1.52, 0.89, 0.88, 1.08, 0.92, 0.88, 1.42, 1.58, 0.88	0.86 to 1.05
	1 Chronic nephritis, hypertension	♀	56	S, 196 D, 98	0.14	—	Electrocardiogram, jugular radial	None used	1.86, 0.65, 0.72, 0.70, 0.72, 0.70, 2.10	0.65 to 0.72
Fevinc	2 Chronic endocarditis, marked decompensation	♂	42	S, 120 D, 90	0.16	++	Electrocardiogram, jugular radial	Arrhythmia first seen after 3 gm of digitalis	0.52, 0.56, 1.14, 0.71, 0.56, 0.51, 0.52, 0.53, 0.55	0.51 to 0.56
	3 Chronic nephritis, chronic myocarditis, hyperthyroidism	♀	10	S, 171 D, 80	0.16 to 0.24	—	Electrocardiogram	Had taken a great deal of digitalis	0.80, 1.52, 0.82, 0.81, 0.80	Absent
	4 Chronic endocarditis, decompensation	♀	25	S, 90 D, 64	0.22 to 0.40	Probable	Electrocardiogram	Had taken a great deal of digitalis		

\* In this column ♂ denotes male and ♀ female

attacks of rheumatic fever. About ten years ago he first noticed his heart thump violently after one of his "spices." This lasted three days. He found that whisky would occasionally bring on these attacks. For the past eight months since an attack of pneumonia, he has been unable to work because of shortness of breath.

On physical examination the patient was found to be a stout rugged man. He sat up in bed, breathing rapidly and with some distress. The tonsils were red and ragged, the pharynx was congested. The heart was markedly enlarged, left border 20 cm to the left of the midsternal line in the sixth interspace. The right border was 4 cm to the right of the midsternal line in the fourth interspace. The action was regular. A systolic murmur could be heard all over the precordium, loudest at the apex. A diastolic murmur was heard along the left border of the sternum, but not at the apex or at the aortic area. Systolic blood pressure was 120, diastolic 90. The lungs showed numerous moist râles in both backs. In the abdomen the liver edge was felt 7 cm below the costal margin in the right midclavicular line. A distinct fluid wave was present. There was marked edema of the scrotum and legs. Patellar, Achilles and plantar reflexes were normal. The Wassermann reaction of the blood was negative. The patient was given a Karrell diet. He took 0.015 gm morphin and was started on 10 cc of an infusion of digitalis three times a day. January 5, two days after entrance, the patient had an attack of transitory auricular fibrillation during which time he felt very much worse. This attack was similar to those he described in his past history. January 29, he was given theocin, and a marked diuresis followed. The digitalis was discontinued for two days from January 29 to January 31, when it was again given in the same doses. February 1 he had two attacks of transitory auricular fibrillation which lasted only a few minutes. Two days later pauses were first noticed which were equal to two heart beats. The electrocardiogram showed this to be sino-auricular block. Digitalis was omitted, February 4, and on this day another paroxysm of fibrillation occurred, but this attack caused no discomfort, for the ventricular rate was slowed as a result of the digitalis action on the heart. From February 9 to March 13, digitalis was given in varying doses almost all the time. Several additional paroxysms were observed, but what were more interesting were the long pauses in the heart action, frequently preceded or followed by an ectopic ventricular beat. During these pauses, which were numerous, all chambers of the heart were inhibited. The length of the pauses was so nearly equal to a simple multiple of the normal heart cycle that it seems probable that there was a blocking of the impulses just below the pace maker. Generally the pause was equal to two beats, but occasionally longer ones were noticed. On one occasion there was total arrest of the whole heart for 3.45 seconds, which equaled five heart cycles. The patient was never bothered by these pauses, although he said that he knew the heart was skipping beats. He did well, his edema disappeared to a great extent, and he was able to walk about. He decided to leave the hospital against our advice. In three weeks he returned to the wards (April 13) in a desperate condition. He had general anasarca and was comatose. After rest in bed, digitalis and the taking of theocin, he recovered so that, May 22, 1915, he left the hospital much improved. During his second stay, he showed evidence of sino-auricular block on only one occasion, and had several paroxysms of auricular fibrillation similar to the ones observed previously. When seen in the outdoor department, Sept 10, 1915, the patient was clinically the same as when he left the hospital, although he has been unable to work.

CASE 3 (Medical No 2218) —A. A., woman, aged 40, complained of cough, palpitation and weakness. Her family history was unimportant. She had had "goiter trouble" for many years, and frequently coughed. Recently the cough and palpitation had been getting worse. When she entered the hospital, January 24, the heart was absolutely irregular, somewhat enlarged and the blood pressure was 174 systolic and 80 diastolic. There were many coarse moist râles

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at both lower portions of the lungs in the back. She showed evidence of hyperthyroidism in that she had exophthalmos, slight tremor of the hands, and a tumor in the region of the thyroid. She was given a great deal of digitalis (47 gm) during the next two weeks. Two days after entrance the auricles stopped fibrillating and the heart action became regular. Several other attacks of transient auricular fibrillation were observed. February 11, pauses of the heart action equal to two cycles were observed which were due to S-A block. At this time the digitalis had also affected the A-V node, causing a P-R interval of 0.24 second. This patient has not been heard from since she left the hospital (Medical Nos 2279 and 2696) —K F W, woman, aged 25, complained of shortness of breath. The family history was unimportant. She had had gradually increasing weakness, palpitation and shortness of breath. Physical examination was unimportant except for the heart, which was enlarged and gave evidence of a constricted and incompetent mitral valve and a relatively incompetent tricuspid valve. The blood pressure was 90 systolic and 64 diastolic. The patient stayed in the hospital from February 4 to April 12, 1915. She took digitalis during this time. The heart rate slowed, and an increase in the P-R inter-

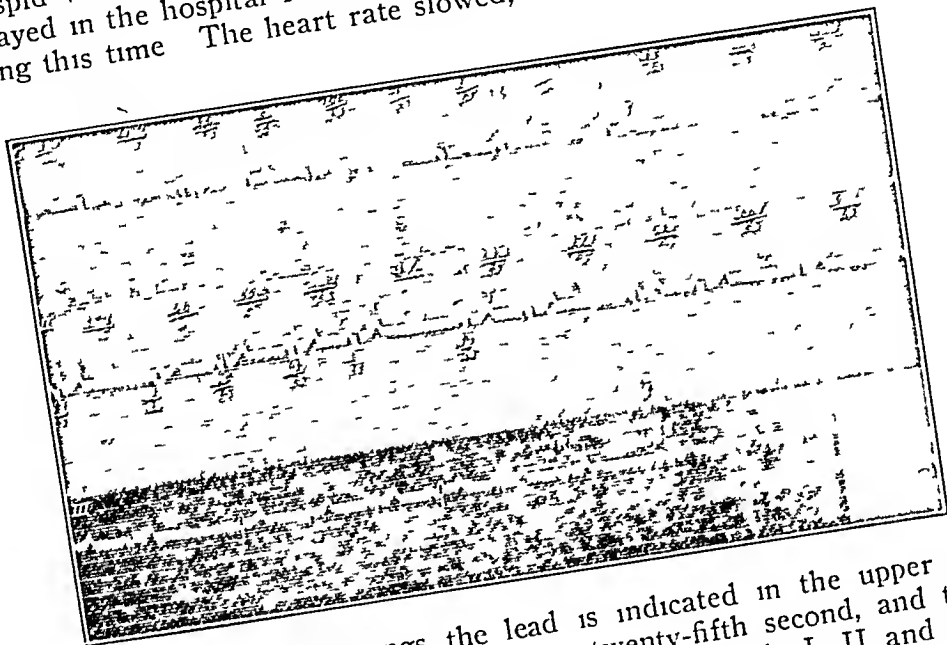


Fig 1—In all these tracings the lead is indicated in the upper left hand corner, the time is in one-fifth and in one-twenty-fifth second, and the deflections are such that 1 millivolt = 1 cm. Case 1, Leads I, II and III, taken Dec 12, 1915, sino-auricular heart block. The figures above the curves are the R-R intervals, those below are P-R intervals.

val occurred. She was again admitted, April 26, 1915, in the same condition as she was in the first time. She was given digitalis again. The length of A-V conduction increased to the extent of a 2 to 1 heart block. May 10, an electrocardiogram was taken which showed not only delayed A-V conduction but also occasional blocked sinus beats. Digitalis had probably affected both S-A and the A-V nodes in this case. Decompensation gradually became more marked, and the patient died, June 20, 1915.

#### EXPLANATION OF THE ELECTROCARDIOGRAMS AND DISCUSSION

Figure 1 gives the electrocardiogram of Case 1 taken by the usual three leads, Dec 12, 1914. With every auricular contraction (P) there is a ventricular contraction (R and T), while during the long pauses no waves appear. The normal heart cycle at this time varies from 0.88 to 1.08 second. This variation could be due to a change in

the rate of the pace maker or to changes in the time it takes the impulse to go from its origin to the auricular musculature. It cannot be entirely due to the latter, for then one would expect the P-P interval to become gradually longer until one sinus beat is blocked. Here the P-P intervals become shorter almost invariably just before a pause, as if the conduction of impulses improve. Occasionally (Fig 1, Lead I third to eighth cycles) the intervals lengthen from 0.88 to 1.07 second, and later shorten without resulting in a blocked beat. One impulse finally is blocked after a short beat. It seems therefore that, although there probably are changes in the S-A conduction, if one is permitted to draw any analogy from the a-v conductive system, these alone are not sufficient to account for the heart block. The other factor is a sinus arrhythmia. When the heart accelerates during sinus arrhythmia, the conduction from sinus to auricle experiences fatigue. Finally, conduction becomes so difficult that sinus impulses are blocked. In this event, we expect the cycle before the blocked beat to be short, and the first one to appear after the block to be long, but on account

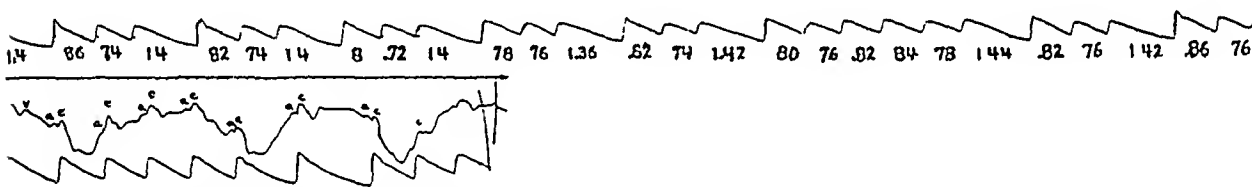


Fig 2 (Case 1) —Radial and jugular tracings taken Dec 12, 1915. The blocked beat is generally preceded by a short cycle and followed by a long cycle.

of the rapid and irregular rate of impulse formation just at the time the beat is blocked, the pause does not equal exactly two normal cycles. These points are illustrated by almost all the tracings taken of the patient over a period of five months, and by many of the other cases in Table 1.

In the polygraphic tracings of Figure 2 there is fairly regular blocking of every third impulse after a cycle of about 0.75 second. The length of the pause averaged 1.40 second, and the cycle after the pause, 0.82 second. If the impulses at this time followed each other in 0.72 second, they would be conducted, but if the interval was shorter for example, 0.70 second, the second impulse would be blocked. The only time that the third beat in Figure 2 was not blocked occurred after a comparatively long cycle, 0.76 second. The ease with which impulses could be conducted was not always quite constant. On other days, impulses were blocked more readily. The shortest cycle that was not blocked in Figure 1 was 0.86 second, which shows that impulses were not conducted as well that day. A point of additional interest is that

when two pauses come in succession, the second is almost always longer than the first (see Fig 1) This follows from the foregoing consideration, that is, as the sinus rate accelerates, a beat is blocked, then one comes through, and the next beat is again blocked, during this time the sinus rate has been gradually decreasing in spite of the fact that the sinus rate is still rapid, and this causes the second pause to be longer than the first

One must consider possible changes in S-A interval as well as changes in the sinus rate If the sinus region is so impaired that some impulses are blocked, it is reasonable to assume that the impulses which are not blocked are transmitted with greater difficulty than normally just as is the case in defective A-V conduction The normal S-A interval is about one-fourth of the P-R interval, that is, from 0.03 to 0.04 second according to Eyster and Meek<sup>6</sup> May it not be that because this interval is so short, it can be greatly prolonged without causing any block? An attempt was therefore made to detect the sinus wave if present and thereby determine the S-A interval Trac-

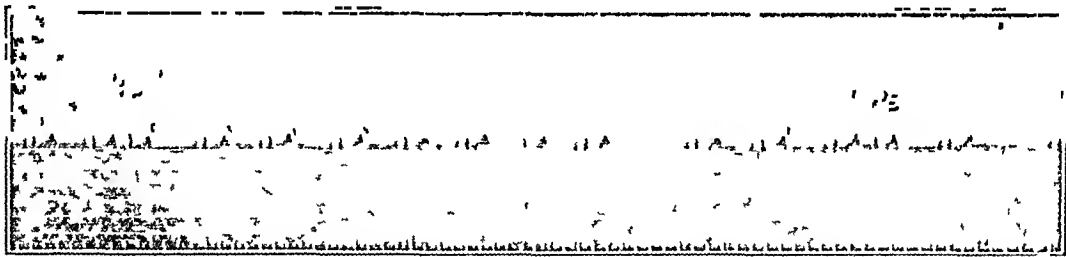


Fig 3 (Case 1) —Lead II, December 15, before exertion Sino-auricular block and occasional premature auricular beats (P B) are present Ventricular rate is 61.16

ings were taken with the fiber standardized so that 1 millivolt was equal to 3 cm deflection and the photographic paper was moving rapidly The peripheral resistance was only 500 ohms, which made it possible to have the string very sensitive and yet not too loose No evidence of any sinus wave could be detected by this means

The rate of occurrence of impulses is one factor which contributes to the incidence of block, and so it follows that if you accelerate this rate, the S-A interval might be lengthened and many impulses would be blocked The patient was therefore asked to lift herself in bed from a reclining to an upright position twelve times Tracings were obtained immediately before and after the exercise (Figs 3 and 4) As was expected, a condition of bradycardia resulted The auriculo-ventricular rate before exertion was 61.16; after exertion the rate for the first twelve beats was 48.52 There were nine consecutive cycles (interrupted only in one place by a short beat) which averaged 1.39 second in length, that is, a rate of 43.17 This result is explained by

supposing that the sinus rate increased and that every second impulse was blocked. As the patient recovered from the exercise and her sinus rate slowed, the number of blocked beats became fewer and she gradually returned to her original condition. The patient herself had observed this phenomenon. She complained that if she moved about, she was more troubled with "jumping heart" than when she remained quiet. The cause of the "jump" was the forcible beat following a long pause. There were more such beats when she exerted herself.

The activity of the vagus nerves was studied to see whether there was any hypervagotonicity or hypovagotonicity present. Figure 5 presents two tracings taken April 23, 1915, showing the effect of right and left vagal pressure. The right inhibited the heart very markedly, while the left inhibited it only slightly. This difference was repeatedly

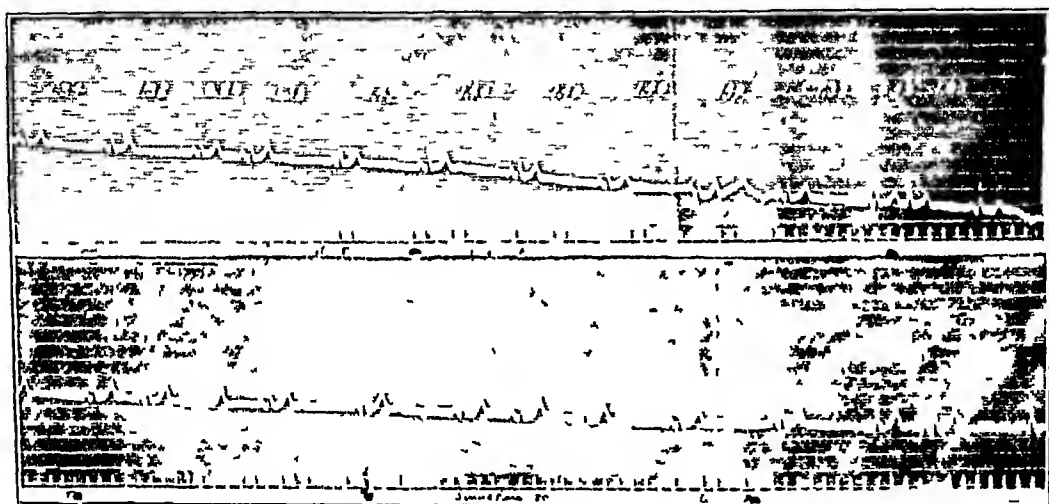


Fig 4 (Case 1) —Lead II, after exertion. Ventricular rate is 43/17. Lower one taken a few minutes later shows return to original condition.

observed. In Figure 5 *a* the first beat after pressure was started is a ventricular beat not preceded by any auricular complex. The beat is supraventricular in origin because of its normal form. The R wave, however, is distinctly higher than the R waves which are preceded by "P" waves, and therefore it is quite probable that an auricular wave is here buried with the ventricular, increasing its amplitude. Similarly the next beat, which comes after a pause of 5.14 seconds, has a higher R wave than the others and is not preceded by a P wave. These are most likely nodal or at least escaped ventricular beats, arising in some supraventricular focus. The following beat, marked P B, is difficult to interpret. It comes prematurely and one might say that the T wave just before is a little different in form from the others, which would be explained by considering that an auricular beat were superimposed on the T wave, that is the auricles had been released from vagal inhibi-

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tion From then on the heart returned to its normal rhythm Left vagal pressure (Fig 5 b) had a much slighter inhibitory effect The second beat after pressure was started is an escaped ventricular beat just as above, but here coming 0.08 second after the auricular beat It is too short a P-R interval to be accounted for by the ordinary conduction of an impulse from auricles to ventricles, especially during left vagal pressure, when there is considerable evidence that the left vagus has a distinct primary negative dromotropic effect on the heart (Robinson and Draper,<sup>27</sup> Levine<sup>28</sup>) The following beat is a similar one except that the P wave comes on the down stroke of the R rather than before it It follows, then, that the auricles and ventricles were contracting independently or that they were responding to the same stimulus arising in the junctional tissue between them It is unlikely that

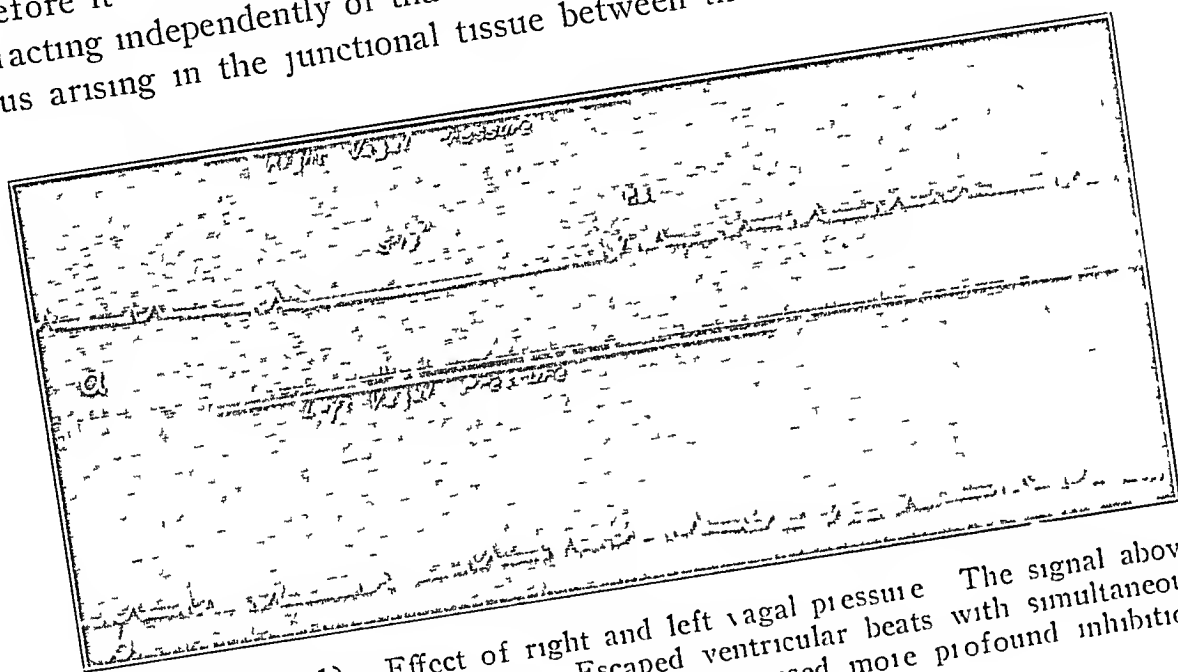


Fig 5 (Case 1) —Effect of right and left vagal pressure The signal above marks the duration of pressure Escaped ventricular beats with simultaneous contraction of auricles are seen The right caused more profound inhibition than the left

they were dissociated, because such beats occurred quite frequently, and one ought to find auricular beats in ventricular diastole

During the second stay in the hospital it was thought that if exercise caused a bradycardia, atropin might have the same effect Two experiments were made on different days The first time 0.001 gm of atropin sulphate was given, subcutaneously, and the second time 0.0015 gm was given The results of the two experiments were practically identical Figure 6 gives a graphic account of the experiment The first

27 Robinson, C G, and Draper, G Action of Vagus Nerve on Human Heart, Jour Exper Med, 1911, iv, 217  
28 Levine, S A The Oculo-Cardiac Reflex, an Electrocardiographic Study with Special Reference to the Difference between Right and Left Vagal and Ocular Pressures in Tabetics and Non-Tabetics, THE ARCHIVES INT MED, 1915, xv, 758



tracing was taken one minute before the injection and shows S-A block. The second tracing of Figure 6 was taken twenty-five minutes after the injection and shows a rapid heart action at the rate of 78 59, and that the heart block has entirely disappeared. The rate increased to 87 a little while later, and at the height of the atropin effect the condition of the vagus nerve was studied to see if there was complete atropin release. Right vagal pressure caused distinct inhibition of the heart (Fig 6, third curve) in spite of the rather large dose of atropin given.

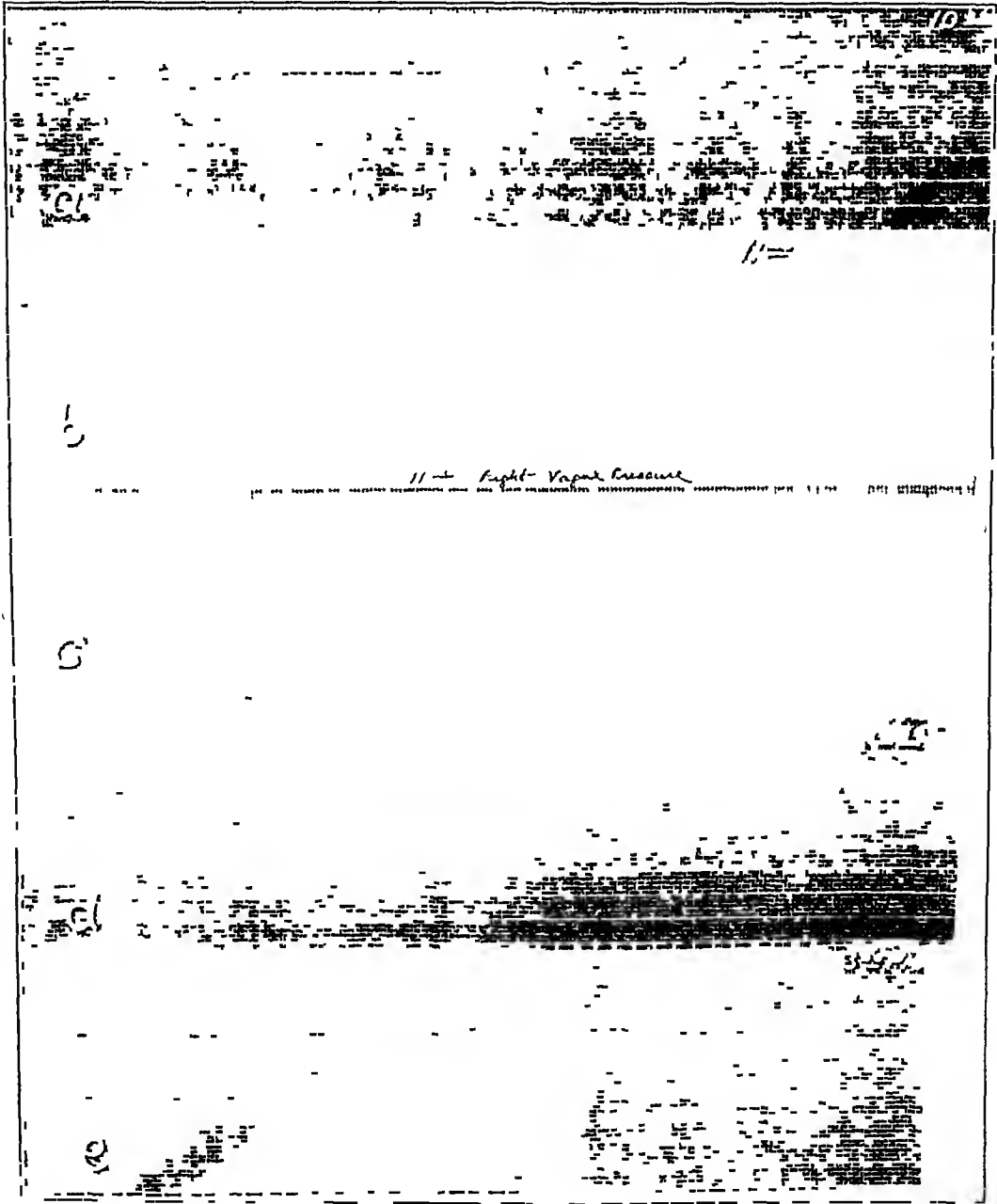


Fig 6 (Case 1) —The course of the heart's action under atropin (taken at the height of the atropin effect) shows that the vagi were not completely paralyzed. Atropin makes the arrhythmia gradually disappear.

Evidently the vagi were not entirely paralyzed by the atropin. The last two tracings of Figure 6 show how the heart gradually returned to its former rhythm. Table 2 gives the apex rate (counted for a minute each time) taken during the experiment.

TABLE 2—APEX RATE

Time	Pulse Rate
10 52	54
Atropin, 0.0015 gm, at 10 57	
11 00	54
11 09	50
11 15	58
11 20	76
11 24	81
11 31	87
11 36	86
11 42	83
11 47	85
11 51	85
11 59	87
12 10	81
12 20	74
12 29	68
12 45	75
1 00	65
2 00	54

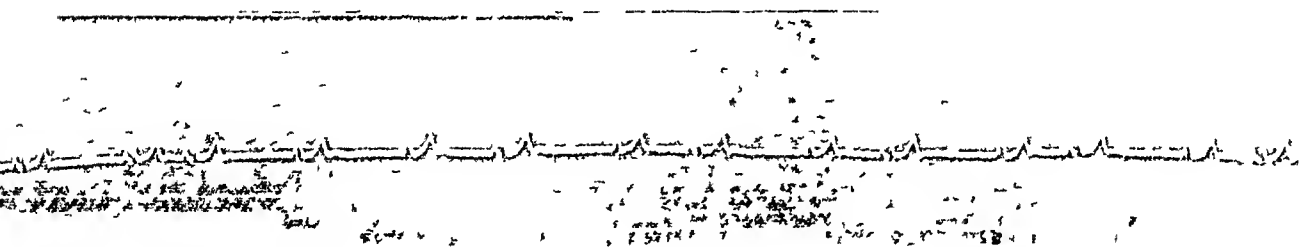


Fig 7 (Case 1)—The signal marks the duration of deep inspiration. Numerous escaped beats probably arising in the junctional tissue appear.

It was expected that acceleration of the rate of the pace maker would result in the blocking of every other impulse as happened after exercise. The explanation suggested for the different result is that atropin increased the conductive power of the S-A node. Ritchie<sup>29</sup> thought that atropin has this effect on the A-V conductive system. On the other hand, the degree of acceleration may not have been sufficient to bring about increased blocking. If the sinus rate had reached 90 or more, block might have resulted.

Holding a deep breath altered the heart's rhythm (Fig 7). The auricular rate decreased. Numerous abnormal beats occurred similar to those of Figure 5. It is evident that the ventricles readily escape

<sup>29</sup> Ritchie, W. T. The Action of the Vagus on the Human Heart, *Quart Jour Med*, 1912-1913, vi, 47.

by starting an inherent rhythm in the absence of impulses coming from the auricles. These beats resemble those recently published by Wilson,<sup>30</sup> which were also obtained under false respiration.

In Case 1, an elderly woman who had hypertension and slight impairment of the kidney functions manifested a persistent arrhythmia which appears to be sino-auricular block. No digitalis was taken at any time. Figure 8 gives a graphic description of the probable time rela-

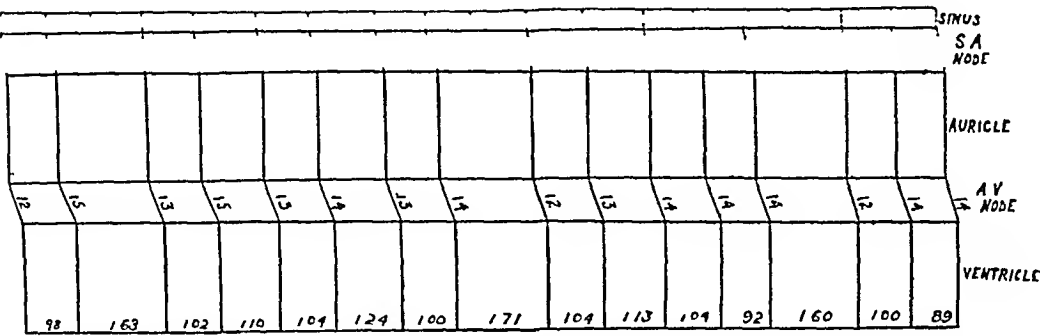


Fig 8 (Case 1)—A diagrammatic representation of a tracing of Case 1, taken April 23. The dotted lines above are the probable sinus impulses with the corresponding S-A intervals. The auricular and ventricular time relations were taken from an electrocardiogram. There is a slight sinus arrhythmia and gradual lengthening of the S-A interval.

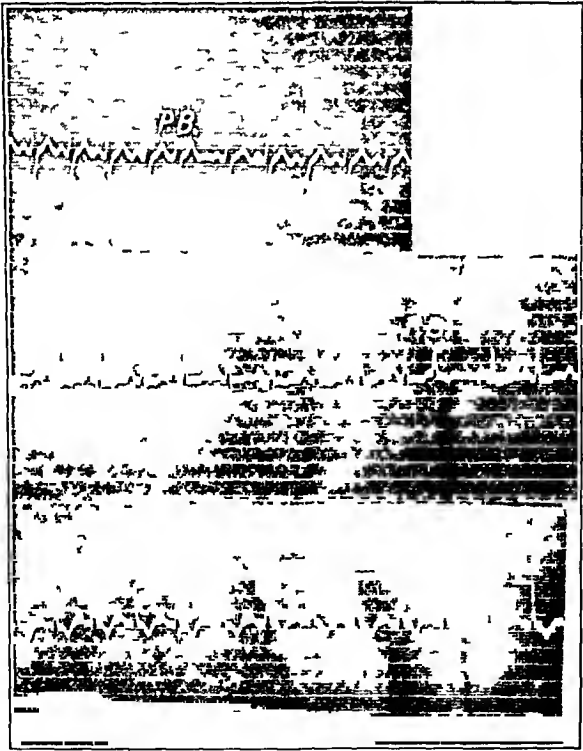


Fig 9 (Case 2), Leads I, II and III—Jan 23, 1915. Premature auricular beats (P B) occur in Leads I and II.

30 Wilson, F. N. Three Cases Showing Changes in the Location of the Cardiac Pace Maker Associated with Respiration, *THE ARCHIVES, INT. MED.*, 1915, *xvi*, 86.

tions of the heart impulses. The auricular and ventricular beats and the P-R intervals were accurately measured. The timing of the sinus impulses and the S-A intervals are hypothetical. The heart was readily inhibited by right vagal pressure, and 0.0015 gm of atropin made the arrhythmia disappear. Exertion, however, caused bradycardia.

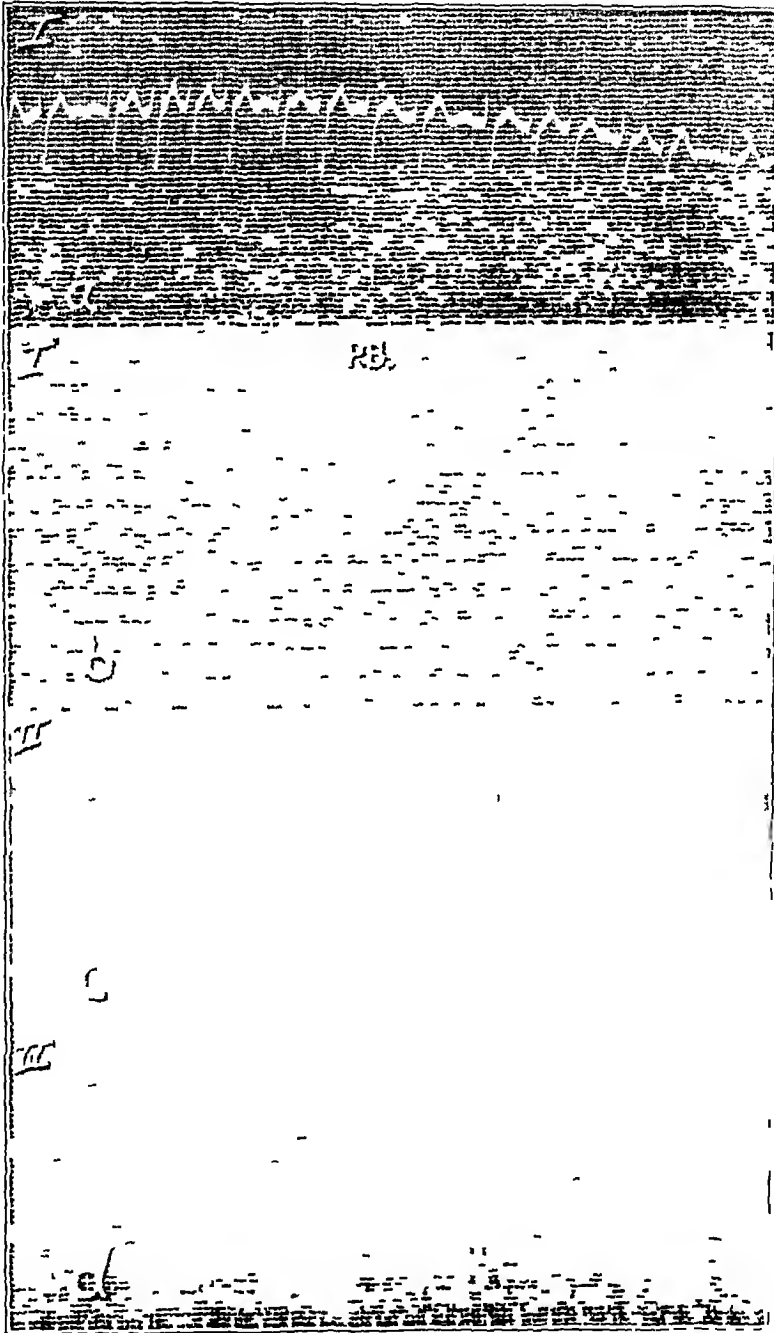


Fig 10 (Case 2) —*a* January 25, 3 p m, shows an attack of auricular fibrillation *b*, January 25, 4 p m, shows a normal heart mechanism except for occasional premature auricular beats, *c*, February 4, 10 a m, shows auricular fibrillation with slow ventricular rate, *d*, February 4, 4 p m, shows a normal heart mechanism

Case 2 showed an entirely different type of sino-auricular block. The heart beat rapidly at the rate of 115.4 (Fig 9). Premature auricular beats (P B) are seen in Leads 1 and 2. The curves indicate pre-

dominant hypertrophy of the right ventricle. The patient had several attacks of transitory auricular fibrillation. Fifty minutes after the attack shown in Figure 10 *a* the auricles stopped fibrillating but developed occasional premature beats (Fig 10 *b*). Between January 25 and February 4 the patient received 3 gm of digitalis. The ventricular rate during the attack of fibrillation, February 4, was 79.8 (Fig 10 *c*), while the rate during the first attack was 139.9. This demonstrates in a striking way the usual effect of digitalis on auricular fibrillation. February 3, a pause of 1.56 second was observed between two P waves which was approximately twice the length of the following beat (Fig 11 *a*). The pause was due to blocking of the impulse at the sinus node. The sinus rhythm was not disturbed. After a premature auricular beat (P in Fig 11 *b*), there was a pause of 1.73 second. This pause

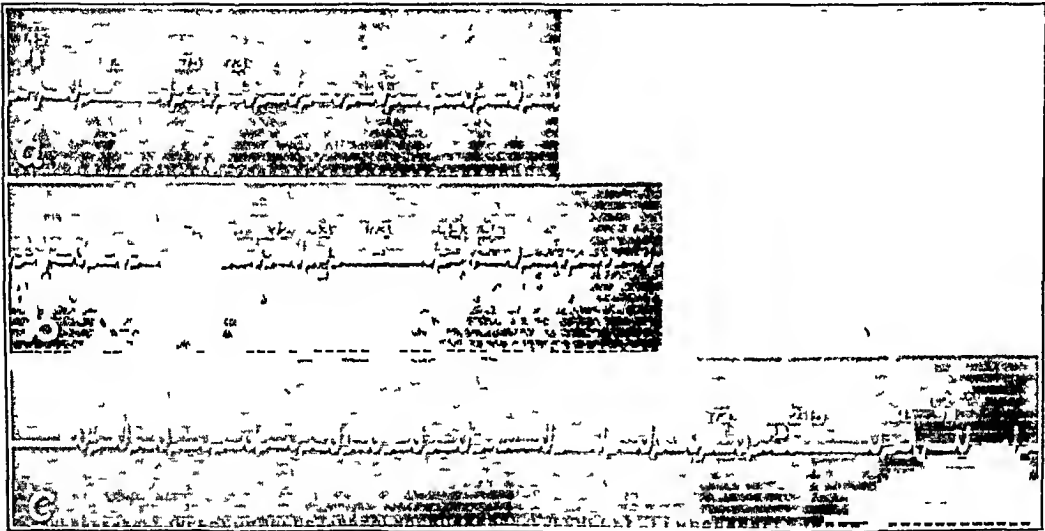


Fig 11 (Case 2) —Numerous pauses due to sino-auricular block, which are generally preceded or followed by a premature beat

consisted of two portions, one due to the preceding premature beat, and the second to the S-A block. The sum of these two intervals, 2.16 seconds, is exactly equal to three times the preceding normal interval, 0.72 second. Frequently after premature ventricular beats, a pause occurred which together with the pause just preceding it equaled 2.15 seconds. This interval is equal to three normal P-P intervals (Fig 11 *c*). Abnormal ventricular beats were almost always followed by sinus blocks. They often recurred directly after the pause. The relation between these ectopic beats and the S-A block is not clear.

Periods of simultaneous sino-auricular block and idioventricular rhythm were also encountered. The auricles beat infrequently, and when that occurred, the ventricles developed their inherent rhythm.  $R_6$ ,  $R_7$ , and  $R_8$  (Fig 12) are idioventricular beats.  $R_9$ , an ectopic ven-

tricular beat, then follows. The slow ventricular rhythm is resumed except for one interruption at  $R_{11}$  up to  $R_{15}$ ,  $R_{15}$  is preceded by a P wave. From  $R_{15}$  on, the auricles and ventricles beat in normal sequence. Figure 12 c shows a very long period of inhibition which resulted from the blocking of four sinus impulses. It illustrates quite clearly that sudden death by "cardiac failure" in some cases might possibly be due to blocking of impulses at the S-A node, with failure of the auricles and ventricles to take up their rhythm.

In Case 2, a middle aged man who had chronic valvular disease showed during the administration of digitalis, which was given him in great quantities, irregular degrees of block at the S-A node. Pauses the length of two, three, four and five normal heart cycles were

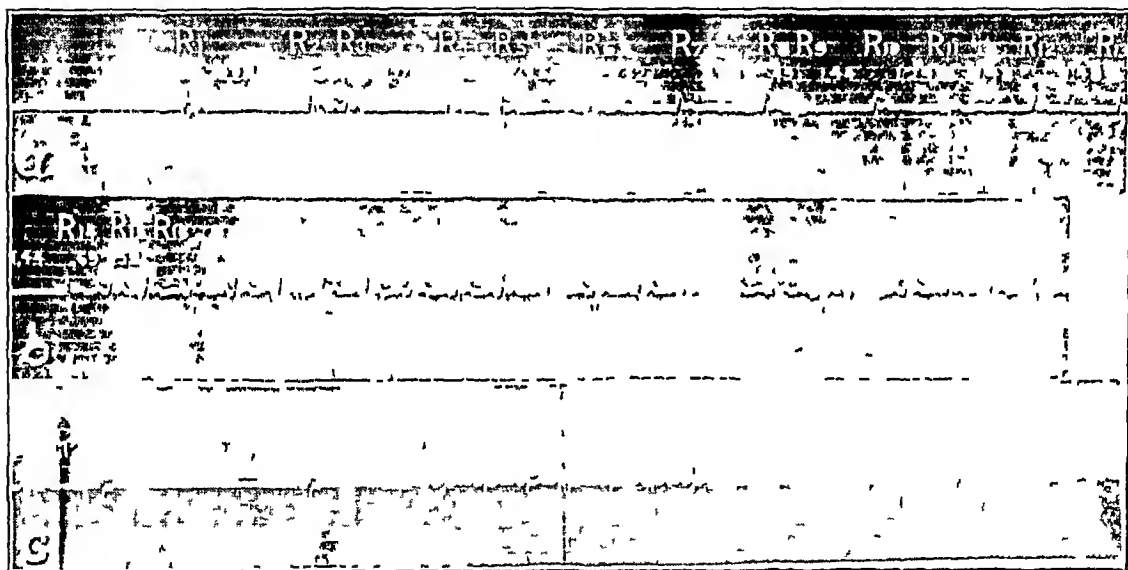


Fig 12 (Case 2) —a and b are continuous. After a long pause, the beginning of which was not photographed, there was complete blocking of sinus impulses for many seconds, except for two interruptions, during which time an idio-ventricular rhythm was started. A tracing taken some minutes later shows several pauses of different lengths, the longest, 345 seconds, resulted from blocking of four sinus impulses.

observed in the electrocardiograms. In one tracing the sinus impulses were blocked over a period of many seconds during which time the ventricles took up a slow regular rhythm of their own. Many of the pauses were related to premature ventricular beats which came immediately before or after the pauses.

Cases 3 and 4 (Figs 13 and 14) are further examples of sino-auricular heart block occurring during the administration of digitalis. Case 3 had attacks of transitory auricular fibrillation as well. Both of these tracings show the effect of digitalis on the A-V system as well as on the S-A node, in the prolongation of the P-R intervals.

Impairment of conduction in the region of the sino-auricular node, then, is not an infrequent result of the action of digitalis. Just as digitalis is thought to have a more marked effect on A-V conduction when the A-V node is damaged, fibrous or other pathologic changes in the S-A node may predispose this site to disturbances such as have been noted in these cases. The relation of this disturbance to auricular fibrillation it is impossible to state. It is significant that two of the four cases here reported, and two of the fourteen cases reviewed here (Laslett<sup>23</sup> and Richbold<sup>24</sup>) had attacks of transitory auricular fibrillation.

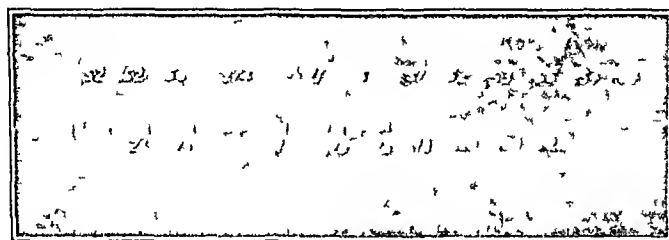


Fig 13 (Case 3) —A blocked sinus beat is shown with a pause of 1.14 second, which is twice the normal heart cycle. The upper figures are the P-P intervals, the lower are the P-R intervals. The P-R intervals are somewhat prolonged (The standardization is photographed at the beginning of the tracing.)

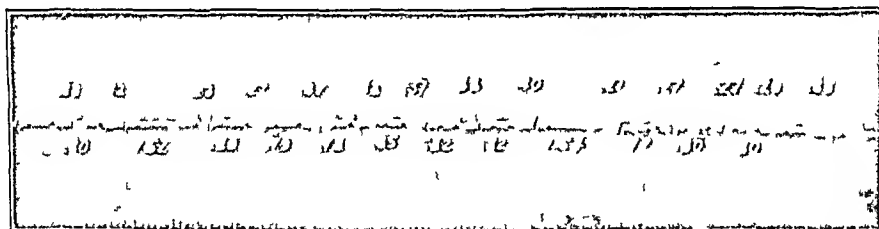


Fig 14 (Case 4) —Two blocked sinus beats as well as prolonged P-R intervals. The upper figures are the P-R intervals, the lower are the P-P intervals. The pauses are slightly less than the length of two normal cycles.

#### SUMMARY

Delayed conduction at the sino-auricular node cannot be recognized until it is of a degree sufficient to cause blocking of impulses. It is probable that the condition of delayed S-A conduction without block is of much greater frequency than heretofore has been thought to be the case. Of the fourteen cases collected from the literature and of the four described here, the arrhythmia was observed after digitalis was given in ten cases, that is, 56 per cent, and it disappeared when the digitalis effects had disappeared in these cases. In four of the other eight cases, it is stated or inferred that digitalis was not given, and in the remaining four no mention is made of the matter. Two of the latter were decompensated and might well have been taking digi-

talís before they were observed. Four cases manifested paroxysmal auricular fibrillation. This suggests that there is some pathologic change in the S-A node which enhances the effect of digitalis. Many of the cases showed a sinus arrhythmia more or less marked. In general, block at the S-A node occurs under the same conditions as block at the A-V node, that is, most commonly as a digitalis effect, also during acute febrile conditions particularly rheumatic fever, and finally in chronic myocarditis.

Four cases are described showing pauses of the heart's action which were equal in length to multiples of the normal heart cycle of the respective individual. There was no evidence of auricular activity during the pauses, which points to a blocking of the impulses above the auricles, that is, at the S-A node. The first case exhibited bradycardia on exertion. The ventricular rate fell to 43 as a result of acceleration of the sinus rate. Tracings taken over a period of five months showed that block depended on a slight sinus arrhythmia. Whenever the sinus rate increased beyond a certain point, the node failed to conduct the impulse to the auricles.

The three other cases showed S-A block only after digitalis had been taken, after it was withdrawn, the block was no longer observed. The second case described showed frequent pauses in which one, two, three or four heart beats were blocked. At one time there was observed in the electrocardiogram a condition of total sino-auricular block for many seconds while the ventricles were beating at their slow idioventricular rhythm.

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# SERUM SICKNESS IN A SERIES OF FIVE HUNDRED PATIENTS TREATED WITH DIPHTHERIA ANTITOXIN<sup>1</sup>

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With a view to ascertaining the frequency and severity of the various symptoms of serum reaction, five hundred patients receiving antitoxin serum were selected from the Louisa Minturn Hospital records. Consecutive cases were used, omitting only patients whose stay in the hospital was less than fourteen days, or whose complications masked the symptoms with which this paper is concerned. The antitoxin used was that dispensed by the New York Department of Health, so that the serum is somewhat modified<sup>1</sup>. Rash was taken as the determining factor in establishing reaction. It seems likely that there are cases which have no rash but give other symptoms, such as malaise, nausea, headache, pains in muscles, slight rise of temperature, etc. It is difficult to group these definitely. They come at the beginning of the second week of diphtheria when the patient begins to sit up out of bed and is put on a more extensive diet, and are associated often with constipation. These factors make the etiology of the mild disturbance difficult to determine. In the following series all patients with pronounced symptoms had a rash, so this forms a convenient and definite starting place.

Of the 500 cases, 422 patients received serum once, while seventy-eight were injected two or more times.

*Frequency of Reaction in Cases Injected Once*—Of the 422 cases receiving one injection, eighty-four or 20 per cent showed symptoms. Previous figures<sup>2</sup> have been from 8.1 to 54.6 per cent. The variations depend on the dosage, the serum itself, and doubtless on the care with which the patients can be watched. The frequency of the reaction increases with the increase in amount of serum given, as is shown by Table 1.

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\* Submitted for publication, Sept 20, 1915.

\* From the Department of Medicine, New York University and Bellevue Hospital Medical College and The Louisa Minturn Hospital.

1 Park, W. H., and Throne, B. *Trans Assn Am Phys*, 1906, **xxi**, 259.

2 Currie, J. R. *The Serum Disease in Man After Single and Repeated Doses*. *Glasgow Med Jour*, 1908, **lxix**, 277.

TABLE 1—SHOWING RELATION BETWEEN DOSE OF SERUM AND NUMBER OF REACTIONS

Number Cases in Group	Number c c Injected	Number Cases Showing Reaction	Per Cent Cases Showing Reaction
20	1 3	3	15
294	4-10	50	17
106	11 15	29	27 35

In addition to the above case one patient received 20 c c and one 50 c c Both reacted

*Day of Disease of Serum Reaction*—The time of appearance of the serum reaction is shown in Table 2

TABLE 2—TIME OF APPEARANCE OF THE SERUM REACTION

Day of Disease	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
No cases whole series	1	1	1	2	8	14	10	25	10	4	1	0	3	2	1	0	1
Receiving under 3 c c					1	1	1										
Receiving 4 10 c c		1		2	6	7	4	15	6	3	1		3		1		1
Receiving 11 15 c c	1				1	6	5	10	3	1				2			
Receiving 20 and 50 c c			1						1								

It would appear that there is no relation between the dosage and the time of appearance within the limits cited

A second reaction was shown by four patients, one on the fifteenth day, two on the fourteenth day and one on the sixth day The latter reacted first on the first day although there was no history of previous injection of serum These cases all occurred in the 1 to 10 c c group

TABLE 3—CHARACTER OF RASH IN RELATION TO SERUM DOSAGE

Dose of Serum, c c	Number Cases	Number Urticarial	Per Cent Urticarial	Number Erythematous	Per Cent Erythematous
1 to 10	53	34	64 15	19	35 85
Over 10	51	29	93 54	2	6 46

*Rashes*—Sixty-three, or 85 per cent of the eighty-four patients had rashes of the urticarial type The remaining twenty-one were erythematous Of the sixty-three urticarial rashes forty-three were severe and general in their distribution, twenty were mild and limited.

two of the severe cases showed small vesicles on the urticarial papules. Grouping these according to dosage, there is seen to be a marked increase in the urticarias with the increase in dose.

*Nausea and Vomiting*—Sixteen patients, or 19.04 per cent, had nausea and vomiting. With increase in the amount of serum given there is an increase in the frequency and intensity of these symptoms.

TABLE 4—SHOWING INCREASE IN THE FREQUENCY OF NAUSEA AND VOMITING WITH INCREASE IN DOSAGE

Dose of Serum, c c	Number of Cases	Number Having Nausea and Vomiting	Per Cent Having Nausea and Vomiting
1 to 3	3	0	0
4 to 10	30	8	16
Over 10	31	8	25.8

TABLE 5—SHOWING DURATION OF VOMITING IN RELATION TO AMOUNT OF SERUM

Amount of Serum, c c	Vomited Once	Nausea 1 Day, Vomited Several Times	Nausea and Vomiting		
			2 Days	3 Days	4 Days
All cases	4	7	2	2	1
4 to 10	3	3	0	1	1
Over 10	1	4	2	1	0

There were no cases of diarrhea. There were three cases of cramp-like pains in the abdomen.

*Edema and Albuminuria*—Four patients had transient edema during the reaction. This is 4.76 per cent. Two of these were in the 1 to 10 c c group and two in the 10 plus group. Three of these involved the eyelids and one the lips. Of the three which showed swelling about the eyes, the tongue also was involved in one and another had at the same time some slight edema about the ankles. Three of the four had a transient albuminuria during the edema. Three other patients of the series had albuminuria without edema, making six in all, or 7.14 per cent.

*Temperature, Pulse and Respiration*—Twenty-five patients, 29.76 per cent, had some rise in temperature. One had a definite chill, 7 patients had rise of 99 to 100 F, 11, 100 to 101, 6, 101 to 102, and 1, to 104. The pulse followed the temperature and the respiration showed little or no change.

*Joints*—Thirteen cases had pain in the joints, 14.28 per cent, 9 of these were of short duration with slight or no local objective symptoms, 4 were severe, with redness, swelling and considerable pain, 2 of these lasted three days, 1, four days, and 1, six days

*Reaction in Cases Receiving Serum More than Once*—Of the 78 cases receiving serum more than once, 60 patients were injected twice and 18 more than twice, 13 of the latter received three injections. There were 5 remaining cases which do not lend themselves readily to grouping. In all of these cases the reinjections were before the appearance of symptoms from the first injection.

The 60 patients injected twice received the serum after an interval of approximately twenty-four hours in every case. In 32 cases the dose was 3, 4, or 5 c c for each injection, so that the total amount of serum received by the patient was from 6 to 10 c c, 8, or 25 per cent, of these reacted. The appearance of the rash was as follows: Two cases the fifth day, 4 the eighth day, and 2 the ninth day. The rash was urticarial in 6 cases, of which 5 were general and severe. It lasted 1 day in 4 instances, 2 days 1 case, 3 days 1 case, 4 days 1 case and 6 days 1 case. There was slight transient albuminuria in one case, 2 patients showed rise in temperature, one to 100, the other to 102 F.

In 28 cases the maximal total dose of the two injections was 20 c c, the minimum 11 c c. In all except 3 the total was 15 c c or more, 10 of these patients, 35.71 per cent, reacted, 7 of the rashes were urticarial. They appeared later than after single or small repeated injections.

TABLE 6—TIME OF APPEARANCE OF THE SERUM REACTION IN REPEATED DOSES

Day of Reaction	6	7	8	9	11	13	14	20
Number of Cases	1	2	1	1	2	1	1	1

It seems from the above that an administration of horse serum in doses from 6 to 20 c c in two instalments twenty-four hours apart is not less likely to give serum reaction than the same amount given in one dose. This seems to hold true also in the small number of patients injected three times. Of 9 who were injected at twenty-four hour intervals with about 5 c c each time, 3 reacted, 2 with a severe general urticaria. Of 4 patients receiving larger amounts, total over 20 c c and under 40 c c, 2 reacted.

Five cases remain which were difficult to classify and from which little can be deduced. They are tabulated below for the sake of completeness.

TABLE 7—ANALYSIS OF FIVE CASES NOT INCLUDED IN ABOVE GROUPING

1st Injec- tion, cc	2d Inj cc	Inter- val Be- tween Injec- tions cc	3d Inj cc	Inter- val	4th Inj cc	Inter- val	5th Inj cc	Inter- val	6th Inj cc	Inter- val	7th Inj cc	Inter- val	Results
20	20	1 day											General urti- caria 3d day, lasted 1 day
2	15	1 day											No reaction
1	12	1 day											General urti- caria 13th day, lasted 2 days
3	10	8 hrs	10	12 hrs	10	1 day	10	1 day	10	2 days	5	2 days	Partial urti- caria 9th day, lasted 1 day
5	20	1 day	20	12 hrs	20	12 hrs	20	9 hrs					No reaction

## SUMMARY

1 A varying proportion of patients receiving modified horse serum react with rash and other symptoms. The larger the amount of serum the larger the number reacting.

2 Most patients react from the fifth to the ninth day, though reaction may take place from the first to the seventeenth day and perhaps later. The time of reaction has no relation to dosage.

3 Rash may be erythematous or urticarial. The larger the dose the greater is the proportion of urticarial rashes. Vesicular urticaria is sometimes, though rarely, seen.

4 Nausea and vomiting occurs in about one in five reacting cases. It is more likely to occur and to be severe and prolonged if the dose of serum is increased.

5 Albuminuria and edema occur occasionally, either together or independently.

6 Joint symptoms occur in about 14 per cent of reacting cases and may be severe.

7 If a given amount of serum be given in two or more doses, it seems not less likely to produce reaction than if given in one injection.

The above cases occurred in the services of the author and his associates in The Lousa Minturn Hospital. To Drs W H Katzenach, Robert J Carlisle, Thomas S Southworth, Edmund L Dow and Stafford McLean, the author expresses his indebtedness for permission to use such of the cases as came in their services.

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## ON NONPARASITIC CHYLURIA <sup>†</sup>

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Ever since the days of the celebrated Physician of Cos, fat in the urine was recognized and its significance discussed<sup>1</sup> In his writings, Hippocrates speaks of several cases of fat in the urine, and mentions the case of a woman who several days after childbirth voided oily urine It is curious to note that while many have written on parasitic chyluria, and some on nonparasitic chyluria, the chemical pathology of the latter variety is shrouded in as much mystery as it was centuries ago

We have attempted briefly to review the literature on this subject, and those interested in the progress of medicine will find, we hope, the following summary of some value<sup>2</sup>

After Hippocrates, who wrote of *fatty* urine and *oily* urine, Galen described three varieties of oleaginous urines, and gave unreasonable methods for their differentiation The physicians that followed the Pergamite for many centuries added very little to his discussion of this subject In the tenth century of the Christian era, the physician Theophile of Salerno in discussing lipuria, stated that the voiding of oily urine was indicative of approaching delirium, convulsions and death The milky color of the urine was ascribed by many authors to the excretion of milk in the urine Actuarius (thirteenth to fourteenth centuries A D), Gordon of Montpellier (*obit* 1320 A D), and others taught that milky or fatty urine signified general febrile conditions and cachexia Other physicians of the sixteenth century wrote that urine rich in fat was a symptom of hectic fever, phthisis and a general decomposition of the body and was a very grave indication of approaching death In 1694 Pez of Paris reported that he had observed the excretion of milk in the urine of a parturient woman, and he thought that this was a normal means of eliminating excessive milk fat from the body

\* Submitted for publication Sept 4, 1915

\* From the Biochemical Department of the Laboratories of the Western Pennsylvania Hospital

1 Hippocrates Aphorisms I, 7 No 35

2 Monvenoux F Les Matieres grasses dans l'urine Paris 1884

The discovery in 1651 by Jean Pecquet of the circulation of lymph caused several authors to offer a different explanation for the appearance of chyluria. In 1670, Valentine Andrea Moellenbrogh wrote a treatise on *Mictione Chylosa*, in which he ascribed chylous urine to an abnormal junction of the urinary and lymphatic systems, but in his description he confused pus in the urine with chyluria, and it was only a century later that Morgagni clearly differentiated the two conditions and gave a scientific discussion of these symptoms.

Pierre Frank (1745-1831) reported a case of chylous diabetes. The patient, a man of 70, voided daily quantities of 16 to 20 liters of urine which much resembled milk. The patient had a very severe thirst and an insatiable appetite. The milky appearance of the urine was not due to pus.

Attempts at the scientific chemical investigation of lipuria began with the dawning of the nineteenth century. In 1817, Alibert<sup>3</sup> described a polyuria which he termed "caseous polyuria." We shall quote him verbatim.

This variety is very rare. I have observed it in two cases. The urine in these cases is of normal daily quantity, and resembles very much milk upon which cream had accumulated. At that time I sent a considerable quantity to the celebrated chemist, Vauquelin, who was kind enough to submit it to a thorough chemical examination. He found in the urine substances which resemble fresh cheese and milk. This phenomenon can not be ascribed to lactation, for both of these women were advanced in years, and one of them never had any children.

The question as to the location of junction—i. e., where the chyle is admixed with the urine—is a mooted one. One group of authorities<sup>4</sup> assumes that the chyle or lymph passes by means of fistulous paths into the urinary system. A necropsy by Ponfick<sup>5</sup> seemed to corroborate this view, but this has been doubted. In a discussion before the *Berliner medizinische Gesellschaft*, Ewald expressed his opinion that the chyle united with the urinary system by means of fistulous connections. Virchow, however, at the same meeting, expressed his skepticism of this view, and said that it was difficult to explain anatomically such a condition of affairs.

Another group of investigators believes that the fat and albumin present in chylous urine are derived directly from the blood. They ascribe this condition to a disturbance of the functional activity of the kidney epithelium which permits of the passage of the abnormal con-

3 Alibert. *Nosologie naturelle*, 1817, 1. Fourcroy and Vauquelin. *Ann de chimie*, 1800, xxxii, 82. Fourcroy. *System des connaissances chim.*, 1801, v, 412.

4 Carter. *Schmidt's Jahrb.*, cxx, 274. Ackerman. *Deutsch Arch f klin Med.*, 1. Dickinson. *Trans London Path Soc.*, xlix, 391. Havelburg. *Virchow's Arch f path Anat.*, ix. Siegmund. *Berl klin Wchnschr.* 1884. Grimm. *Ibid.*, 1885.

5 Ponfick. *Schmidt Jahrb.*, clxix, 4.

stituents into the urine They also found that the blood was very rich in fat in this disease <sup>6</sup>

In 1884 Wilson<sup>7</sup> claimed that he had isolated an organism from the urine of patients suffering with chyluria which he thought was the causative factor of this disease This observation has never been corroborated, and in fact many aspersions have been cast on the reliability of his findings

In 1891, Wolff,<sup>8</sup> in his dissertation on this subject drew the following conclusions from his study of a case of chyluria and from the report of Goetze's findings <sup>9</sup> Chyluria is certainly not due to disease of the liver The secretion of chyle into the urine stands in no relation with fistulous passages between the lymphatic and urinary tracts The fat and the albumin in the urine are directly excreted from the blood into the urine through the kidneys

The references in this paper will show the number of investigators who have, mostly superficially, studied this condition <sup>10</sup> We find that this disease has no predilection for either sex The average age of the patients is about 40 years No disease or condition of health seems to predispose to this disturbance In fourteen cases reviewed by Monvenoux we find diabetes in one, bad alimentation in two, debility in two, and blennorrhagia, menopause, parturition, hemiplegia, chorea and lymphorrhagia in as many individual cases Veis described a case in which chyluria was noticeable during pregnancy The pregnancy was forcibly interrupted rather because of the excessive albuminuria than because of the chyluria Chyluria may be unilateral as was reported by Israel<sup>11</sup> and others Davis<sup>12</sup>

6 Eggel Deutsch Arch f klin Med, xiv, 449 Thudichum Schmidt's Jahrb, cxxiv, 270 Bence-Jones Philosoph Trans, 1850, v, 930 Brieger Ztschr f physiol Chem, iv Cohnheim Vorlesungen u allg Pathol ii, 384

7 Wilson Lancet, London, 1884, p 1128

8 Wolff, H Zur Lehre von der Chylurie, Dissertation, Berlin, 1891

9 Goetze Die Chylurie, Jena, 1887

10 Prout Ann Philosoph, xiii, 20 Nasse Unters z Physiol u Path, 1835, p 211 Bence-Jones Med-Chir Trans, xxxiii, xxxiv Waters Ibid, 1862, 45 Begbie Edinburgh Med Jour, 1862, viii, 132 Beals See Monvenoux (Note 2), p 279 Morgan Ibid, p 285 Roberts A Practical Treatise on Urinary and Renal Diseases, London, 1872, p 327 Dickinson Med Times and Gaz, 1877 ii 659 Ord, Miller Trans Path Soc, London 1878, xlix, 402 Baibour Glasgow Med Jour, 1879 xi, 21 Bouchut Gaz d hôp, 1879, lii, 847 Melu L'Urine, p 221 Guyon Traité clin sur les Malad des voies urin, Paris, 1881 Boissard France med, 1882, xlix, 410 Brieger Berl klin Wchnschr 1885 p 405 Oliver Bull Soc D'Anthropolog Paris 1878, i, 44 Ackermann Deutsch klin, 1863, p 23 Ralfc Med Times and Gaz, 1877, p 571 Frank Wien med Wchnschr July 1, 1909 Salle Deutsch Med Wchnschr, 1909, xxxv 142 Haatek Deutsch med Wchnschr 1910, xxxvi, 794 Veis Berl klin Wchnschr 1905 xl 27 Davis Am Jour Obst and Dis Women and Child 1913, lxxiii 3

11 Israel Mitteil a d Grenzgeb d Med u Chir 1903 ii 171, 217

12 Davis Am Jour Obst and Dis Women and Child 1913 lxxiii, 3



reported a case of chyluria in a pregnant woman. The patient had an uneventful pregnancy and was delivered at full term. The phenol-sulphonephthalein test on the right and left kidneys showed that they functionated equally well.

Through the courtesy of Dr. Thomas T. Kirk of Pittsburgh we were enabled to make a careful study of the following case of chyluria. The history of the case will be found toward the close of this paper.

The patient, who had given birth to a child four months before this study was undertaken, complained of five main symptoms: Chyluria, polyuria, polydipsia, polyphagia and some loss of weight. These symptoms would make one think first of all of diabetes. The findings, however, have proved conclusively that this was not the case. The fact that she had lived for the past quarter of a century in Pittsburgh proper, and the fact that we could never find any parasite in her blood or urine, prove that this is a case of nonparasitic chyluria. The following is a report of the chemical and microscopical investigations that have been made on this patient.

#### THE URINE

*Quantity*—The patient voided daily quantities of about 3,000 c c. Latterly, however, the quantities daily voided have been less, the quantity fluctuating between 1,550 and 1,760 c c. The patient declares that before she came to the hospital she was voiding very much more urine than she is doing now.

*Color*—The urine varied in color from yellowish white to cream color. The separate specimens collected during the various hours of the day showed differing appearances. In the morning the urine was amber, but smoky, toward the afternoon the urines showed streaks of red. In general, the urine collected as a twenty-four hour specimen on several successive days resembled yellowish milk.

*Odor*—The fresh urine was almost odorless or had the normal uriniferous smell. On standing for a few hours the urine became strongly ammoniacal, so that we used a few crystals of thymol to preserve the urine.

*Specific Gravity*—The specific gravity varied between 1.005 and 1.011. The morning specimens had a higher specific gravity than the total twenty-four hours mixed sample.

*Appearance*—The urine was entirely opaque. On centrifugalization a sediment of fibrin and blood appeared at the point of the centrifuge tube, but no lessening of the opacity resulted, showing that the emulsion was a very fine one and permanent. The urine did not change in appearance when allowed to stand in the ice box.

for several days. White and reddish masses were observed in the twenty-four-hour specimens. These masses will be described under the heading *Protem*.

*Reaction*—The reaction of the urine varied. It was usually neutral to litmus. However, on titrating the urine with decinormal sodium hydroxid, using phenolphthalein as an indicator, by Folin's method we found an acidity equal to 1.7 to 2.4 c.c. tenth normal sodium hydroxid for 10 c.c. of urine.

Filtration had no effect on the appearance or the color of the urine. But when the urine was shaken with ether and allowed to separate, it became amber in color, cloudy in appearance, but it had lost very much of its opacity. The urine after ether extraction was tested for albumin and found to be positive. After coagulation of the albumin and filtration, the urine was found to be clear, amber, and to all appearances looked like normal urine.

*Protem*—The quantity of protein present in the twenty-four hour specimens varied. By Scherer's method the average figure obtained for three successive days was 3.1 parts per thousand. The Tsuchiya method gave a much lower figure of 2.7 parts per thousand. Solidified masses of fibrin and albumin were found in the urine. Some of these masses were almost pinhead in size and reddish in color, other masses were of the size of walnuts. No albumose was found. By fractional precipitation with ammonium sulphate both globulin and albumin were found.

*Mucin*—Certain of the masses present in the urine had a gelatinous appearance, were stringy and gave tests for mucin. These mucin masses varied in quantity on different days. That these masses came from the urinary tract and were not admixtures from the genital passages is certain, for they were found in catheterized specimens.

*Glucose*—The urine did not contain any glucose. Fermentation tests of the chyle urine and of the urine after the fat and the albumin had been removed gave negative results. The reduction tests were negative. No osazone could be formed. Tests for lactose, pentose and levulose gave negative results. No lactic acid was present.

*Leucin, tyrosin, or cystin* could never be demonstrated in any specimens of urine.

Traces of *indican* were always present.

*Cholesterol*—The excretion of this substance varied considerably. In the first specimens of urine obtained from the patient some time ago the cholesterol was easily detected. Lately, however, cholesterol has decreased in the urine. The cholesterol was determined by the method of Weston and Kent<sup>13</sup>. The daily excretion varied in the

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13 Weston and Kent Jour. Med. Research, 1912, xxi, 531

early course of the disease from 0.4 parts per thousand to 0.85 parts per thousand

Neither lecithin nor cholin could be detected in the urine

Acetone, diacetic acid and beta-oxy-butyric acid were always absent

*Microscopic Appearance*—On examination of a centrifuged specimen, many red and white blood cells could be observed. Globules of fat of the size of ordinary milk globules were seen. These fat particles stained red with Sudan III. Triple phosphate crystals were usually present. Occasionally a crystal of cholesterol was observed. No granular or blood casts were ever noticed, though a thorough search was made for them. A few hyaline casts were usually present. Repeated painstaking examination for filaria or any other parasite proved futile. These examinations were made on specimens collected at different times during the twenty-four hours. Occasional squamous epithelial cells were seen. The bacterial findings were negative. Special examination for the tubercle bacillus gave negative results.

The elimination of nitrogen, sulphur and phosphorus was studied. The nitrogen partition reveals the fact that there is a large increase in the purin bases and creatinin excretion. This increase seems to be fairly constant. The ammonia nitrogen seems normal. The output of urea is decreased.

The accompanying table (Table 1) is the result of the determination of nitrogen partition on three successive days.

In the sulphur partition, which was done on the same days as the nitrogen partition, we found an increased neutral sulphur fraction. The total sulphur output seems normal. The inorganic sulphates are reduced, whereas the ethereal sulphates are also increased. Table 2 incorporates the results of this partition.

The phosphorus partition seems to be entirely normal so far as could be determined. The average daily excretion of phosphorus calculated as phosphorus pentoxid was 2.1084 gm (analyses made on three successive days).

Not long ago, Young<sup>14</sup> had occasion to study the protein metabolism in two cases of chyluria. The first patient was a woman 42 years of age, who, though otherwise healthy, had noticed that her urine became milky in appearance, and clotted into jelly-like masses on standing. She had pains in her lumbar region which were dull and aching in character, and she had observed that her urine was stained with blood. No parasites were ever found in the blood or in the urine. The second patient was a miner, 23 years old. For eight years he had been passing urine which was blood stained and which on standing became milky and had jelly-like masses. No filaria were

<sup>14</sup> Young Jour Trop Med and Hyg, 1914, xvii, 241

TABLE 1—NITROGEN PARTITION IN URINE

Day	Total N gm	NH <sub>2</sub> N Per Cent Total N	Urea N Per Cent Total N	Uric Acid N Per Cent Total N	Purin N Per Cent Total N	Creatinin N Per Cent Total N	Rest N Per Cent Total N	Quantity of Urine cc
1	14 7294	3 74	72 06	2 71	3 05	4 17	14 27	1,670
2	14 8107	3 42	73 37	2 14	3 17	3 82	14 04	1,980
3	12 9413	3 55	73 33	1 98	3 35	4 05	13 74	1,770
Average	14 1203	3 57	72 92	2 27	3 19	4 01	14 01	1,806

TABLE 2—URINARY SULPHUR PARTITION

Day	Total S gm	Inorganic Sulphate Per Cent Total S	Ethereal SO <sub>4</sub> Per Cent Total S	Neutral S Per Cent Total S	Volatile Sulphids	Quantity of Urine cc
1	2 107	38 4	23 78	37 82	Normal	1,670
2	2 291	36 7	23 86	39 44	Normal	1,980
3	2 088	32 5	30 79	36 71	Normal	1,770
Average	2 162	35 8	26 14	37 99		1,806

found in this case. The fat content of the urine was 1.8 per cent in the first case and 2.6 per cent in the second case. The quantity of protein nitrogen excreted daily varied in the first case from 0.49 to 1.94 gm, the average for the fourteen days of observation being 0.95 gm per diem, corresponding approximately to 6 gm protein. In general this patient showed a lowered nitrogen metabolism. In the second case the daily loss of protein nitrogen averaged 2.4 gm equivalent to about 15 gm protein. When, however, the diet was liberal and controlled only by the appetite of the patient, the quantity of nitrogen excreted decreased steadily, the nonprotein nitrogen falling as low as 6.1 gm daily, corresponding to only 38 gm protein catabolized, a figure below normal. The protein nitrogen excretion was still on the decline when the observations of the metabolism were discontinued.

*Urmay Fat*—The quantity of fat varied in the daily specimens. In the early course of the disease it was much more than later on. Determinations by the Babcock method gave figures on successive days that fluctuated between 3.8 per cent and 5.4 per cent. One evening sample yielded as much as 6 per cent fat. Analysis by the Soxhlet method gave slightly smaller results, varying on various days between 3.2 per cent and 5.1 per cent.

On shaking the urine with ether, the urine became demulsified and the ethereal extract was separated. The ethereal extract was of a canary yellow color. On driving off the ether a clear, limpid, yellow oil was obtained. It gave the characteristic "grease spot" on paper. Acrolein test was positive. The melting point of this crude oil was found to be 35.5 C. It was decided to extract a large quantity of fat and determine its composition.

The urine was dried with plaster of Paris and extracted with ether for seventy-two hours in a Soxhlet apparatus. The ether was then evaporated and the fat obtained. It was found that the fat was composed of two portions. One was soluble in alcohol and the other portion was not.

*Alcohol soluble portion* was obtained by evaporating the alcohol on a hot plate. An oil was obtained. It is soluble in warm alcohol, ether, chloroform, xylol, toluol and acetone. It separates out from the alcoholic solution when immersed in a freezing mixture. The oil is liquid at ordinary temperature. On immersion in a freezing mixture it solidified at -5 C. This oil was easily saponified by potassium hydroxid. The acid obtained by this method proved to be oleic acid, as determined by the melting point of the crystals (13.5 C) and the Hubl iodine number. The acid was insoluble in water, but soluble in ether, chloroform and alcohol.

The alcohol insoluble portion is a white, opaque, greasy substance. It is solid at ordinary room temperature. While it is not soluble in cold or slightly warmed alcohol, it was found to be soluble in boiling alcohol. The fat crystallized on cooling the alcoholic solution<sup>15</sup>. The crystals obtained were rather irregular. They formed clumps from which projected long thin plates or needles. The melting point of several samples obtained on different days varied between 58 and 65 C. From its melting point and from its crystalline appearance we believe this fat to be margarine. On saponification with potassium hydroxide we obtained crystals of fatty acids which resembled both stearic and palmitic acids.

*Functional Tests of Kidneys*—Ureteral catheterization of both kidneys showed that fibrin clots and blood were present on the left side but absent on the right. This was not, however, a constant observation.

The accompanying comparison (Table 3) of the urines of the right and left kidneys is the result of one observation. Several other examinations with catheters at different periods gave other results (see later).

TABLE 3—COMPARISON OF URINES FROM RIGHT AND LEFT KIDNEYS

	Left Ureter	Right Ureter
Color	Amber yellow	Straw
Albumin	Heavy	Heavy
Reaction	Neutral	Acid
Fibrin	Present	Absent
Benzidin test	Positive	Negative
Red blood cells	Many	None
White blood cells	Many	Few
Casts	None	Few hyaline
Fat	Present	Present
Cholesterol crystals	Present	Absent
Ova and parasites	Absent	Absent

*The Phenolsulphonephthalein Test*—This test was carried out twice on the patient. The first time was during the week when the patient was on a fat-poor diet. Both ureters were catheterized with the following results. It was found that the right kidney secreted during the same period five times as much urine as the left. The red color appeared in the right kidney in seventeen minutes, whereas in the left kidney the color was very faint and appeared only in twenty-six minutes. The amount of phthalein in the right

15 The cholesterol was separated from the oil by pipetting off the supernatant oil, which remains fluid at room temperature.

kidney (half hour's collection) was 3 per cent , and in the left kidney there was less than 1 per cent The urine examined after ureteral catheterization of both kidneys gave the result shown in Table 4

TABLE 4—PHENOLSULPHONEPHTHALEIN TEST

	Right Kidney	Left Kidney
Phenolsulphonephthalein	3 per cent	Less than 1 per cent
Albumin	Very faint	Moderate
Fat	None	None
Red blood cells	None	Rarely
White blood cells	Rarely	Many
Casts	None	None
Epithelial cells	Few	Few
Parasites	None	None

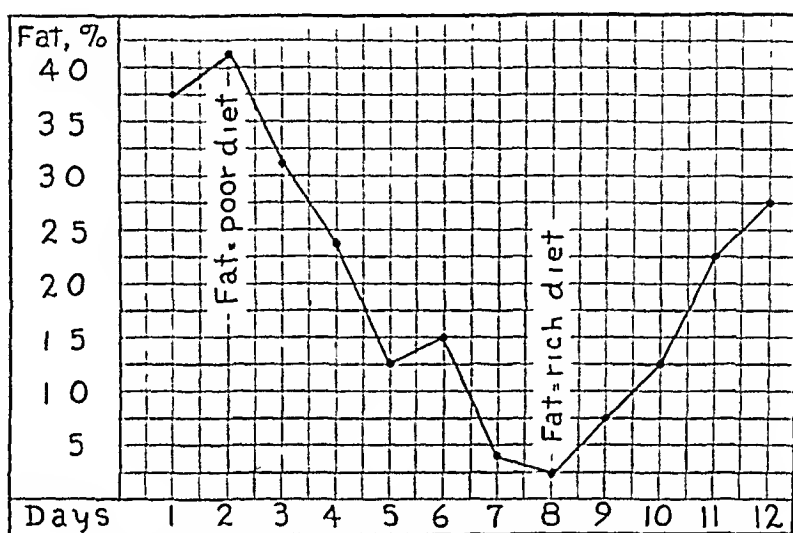
The phenolsulphonephthalein test was performed a second time during the period when the patient was on a fat-rich diet The ureters of both kidneys were catheterized and the phenolsulphonephthalein collected It was observed that the right kidney secreted in forty minutes 110 c c of urine, whereas the left kidney secreted only 6 c c Table 5 gives a comparison of the urine from the right and left kidneys

TABLE 5--COMPARISON OF URINES FROM RIGHT AND LEFT KIDNEYS

Before the Phthalein Test	Right Kidney	Left Kidney
Color	Yellowish	Watery
Appearance	Very cloudy	Faintly cloudy
Reaction	Acid	Acid
Albumin	Moderate	Heavy
Fat	Very much	Slight
Cholesterol	Present	Present
Glucose	None	None
Red blood cells	Many	Many
White blood cells	Many	Moderate
Epithelial cells	Many cuboidal	Many cuboidal
Casts	None	None
Parasites	None	None
After the Phthalein Test (Forty Minutes)		
Amount of urine collected	110 c c	6 c c
Phenolsulphonephthalein	8 per cent	Less than 1 per cent

*Influence of Diet on Fat Excretion in the Urine*—The patient was kept on a diet poor in fat for a period of eight days, and it was found that the fat excretion was much reduced The urine which was voided in the early morning was especially poor in fat,

was faintly cloudy and resembled very closely a urine with a moderate amount of phosphates. The amount of fat on two successive days in the twenty-four-hour specimen of urine collected on the sixth and seventh days that the patient was kept on this diet was 0.47 per cent and 0.25 per cent, respectively. The accompanying curve shows the fat excretion on this diet. The amount of albumin excreted was also somewhat diminished. Blood in the urine was present only in small streaks.



Fat excretion on fat-free and fat-rich diets

A diet rich in fat caused the following symptoms to appear in the urine. The early morning specimen was very cloudy, in fact much more cloudy than any individual specimen that was obtained during the previous course of the disease. The urine was milky and rich in fat, the morning specimen contained 2.14 per cent on the third day, as determined by the Babcock method. Very much wax-like material was present as well as mucin.

In 1858 Thudichum<sup>16</sup> wrote about chylous urine as follows:

The urine is oftener fatty when the patient subject to this disease lives on an animal diet than when he eats a more vegetable one. It is most clear before breakfast and most fatty after dinner. It is oftener free from fat before breakfast, when the diet is vegetable, than when it consists more of animal food. Fat passes off in the urine after food is taken, yet the albumin, fibrin and blood globules are thrown out before any food has been taken. During perfect rest the albumin ceases to be excreted, and it does not appear in quantity in the urine even after food is taken, provided there is perfect rest. The disease of the kidney permits fibrin, albumin globules and salt to pass whenever the circulation through the kidneys is increased, if at the same time fat is present in the blood, it escapes also into the urine.

#### THE BLOOD

An examination of the blood showed hemoglobin 78 per cent, leukocytes 5,400 and erythrocytes 4,200,000. Differential leukocytic

<sup>16</sup> Thudichum. A Treatise on the Pathology of Urine, London, 1858, p. 240.



count gave the following average results Polynuclears 77 per cent, lymphocytes 15 per cent, large mononuclears 7 per cent, eosinophils 1 per cent No eosinophilia was ever found The blood was searched on many occasions, and in specimens taken at different hours of the day, for parasites but none were found The fat in the blood was only slightly increased The urea in the blood was normal Sugar was found to be 0.85 parts per thousand The cholesterol content was very high—3.2 parts per thousand of blood serum

#### THE FECES

The patient was usually constipated so that a laxative had to be administered The feces thus obtained was soft, normal in color and odor The fat content was quite normal Bile pigment was present Blood was absent No parasites or ova could be found

#### CLINICAL EXAMINATION OF PATIENT

Both kidneys were repeatedly catheterized No obstruction was found Cystoscopy and ureteroscopy gave negative results Several Roentgen-ray examinations were made but nothing abnormal was found There were no fistulous passages that could be found and no abnormality in the kidney shadows

An exploratory operation did not reveal any abnormality that was noticeable in the anatomy or situation of the kidneys The blood vessels leading to and from the kidneys were normal The ureters were normal

#### HISTORY OF THE CASE

Mrs. A. S., housewife, aged 42, born in Germany At the age of 13 she came to the United States, and with the exception of her first year's residence in New York, she has always lived in Pennsylvania She has been married twelve years Her menstrual history is normal She has four children living The oldest is 10 years and the youngest is 4 months old Labors and puerperium were normal Her family history is absolutely negative About seven years ago her urine for a few months was of a reddish brown color, containing blood clots and occasional white curds At that time she also complained of weakness and vertigo Otherwise she has always been healthy The present illness began on the third week after childbirth, about fifteen weeks prior to examination She voids a milky urine of excessive amount, she has a ravenous appetite, and a sensation of emptiness in her stomach She is continuously thirsty She has lost considerable weight since the confinement She has never complained of any obstructive pain in the urinary tract

#### CONCLUSION

It would seem that this is a case of nonparasitic chyluria Abundant evidence has been furnished that there is no pathologic structural connection between the lymphatic system and the urinary tract It would appear that the chyluria in this case was due to a passage of fat from the blood directly into the urine through the kidney epithelium, caused, probably, by a functional disturbance of the kidney cells

# EXPERIMENTAL ALCOHOLIC CIRRHOSIS OF THE LIVER<sup>1</sup>

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Ever since the experimental method has been used in pathology numerous attempts have been made to show the connection between cirrhosis of the liver as often seen in "steady drinkers" and alcohol as the causative factor. In this experimental work alcohol has been used subcutaneously, intravenously, by inhalation, and fed by mouth. Ethyl alcohol has been used by most all, but some have used amyl and methyl alcohol, while others have used mixtures of these, and still others have used various beverages, such as schnapps, brandy and absinthe. Rabbits, guinea-pigs, dogs, rats, mice, hens, cats, ducks and pigeons have been used as experimental animals. Dahlstrom,<sup>1</sup> Duchek,<sup>2</sup> Joffrey and Serveaux,<sup>3</sup> von Baumgarten,<sup>4</sup> and de Rechter,<sup>5</sup> were among the first to carry out work along these lines, but with negative results. Ruge,<sup>6</sup> Magnan,<sup>7</sup> Kremiansky,<sup>8</sup> Mairet and Cambermale,<sup>9</sup> Afanassiew,<sup>10</sup> v. Kuhlden,<sup>11</sup> Friedenwald,<sup>12</sup> d'Amato,<sup>13</sup> Strass-

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<sup>2</sup> From the Laboratory of Pathology and Bacteriology, Medical School State University of Iowa

1 Dahlstrom. Cited from Fahr, Note 23

2 Duchek. Alkohol im tierischer Organismus, Prager Vierteljahrs, 1853

3 Joffrey and Serveaux. Mensuration de la toxicite vraie de l'alcool, Arch de med exper et d'anat path, 1897

4 v. Baumgarten. Ueber die durch Alkohol hervorgerufenen pathologisch-histologischen Veränderungen, Verhandl d deutsch path Gesellsch, 1907

5 De Rechter. Bull de l'Acad roy de med Belgique, 1892

6 Ruge, L. Wirkung des Alkohols auf den tierschen Organismus, Virchows Arch f path Anat, 1870, xlix

7 Magnan. Alcoolisme aigu, etc, Compt rend Acad d sc, 1869, p 825

8 Kremiansky, J. Ueber Pachymeningitis interna hemorrhagica bei Menschen und Hunden, Virchows Arch f path Anat, 1868, xlii

9 Mairet and Cambermale. Compt rend Acad d sc, 1888, Nos 10, 11 and 12

10 Afanassiew, W. A. Zur Pathologie des akuten und chronischen Alkoholismus, Beitr z path Anat u z allg Path, 1890, viii

11 v. Kuhlden. Cited by Fahr, Note 23

12 Friedenwald. Pathological Effects of Alcohol on Rabbits, Jour Am Med Assn, 1905, xlv, 780

13 d'Amato. Ueber experimentelle, vom Magendarmkanal aus hervorgerufene Veränderungen der Leber und über die dabei gefundenen Veränderungen der übrigen Bauchorgane, Virchows Arch f path Anat, 1907, clxxxvii

man,<sup>14</sup> Pupier,<sup>15</sup> and Bischoff<sup>16</sup> in their early work at least got only parenchymatous degeneration of the liver cells as a result. Dujardin Beaumetz and Audige<sup>17</sup> fed hogs with their food, alcohol in the form of wood alcohol, malt spirits, beef spirits, potato spirits and absinthe. This experiment lasted three years, but owing to the large amount of interlobular connective tissue naturally present in these animals it was not a success.

Straus and Blocq<sup>18</sup> fed rabbits ethyl and amyl alcohol by means of a stomach tube and obtained cirrhosis after three months. Pupier<sup>15</sup> claimed that experimenting with hens he got an interstitial hepatitis with absinthe, hypertrophic cirrhosis with red wine and atrophic cirrhosis with white wine. Afanassiew<sup>19</sup> gave dogs, rabbits, guinea-pigs, and white rats, by means of a stomach tube, a mixture of ethyl and amyl alcohol, and in some instances obtained a well marked cirrhosis. He also injected alcohol into the portal vein of dogs with positive results. De Rechter<sup>5</sup> got similar results. Mertens<sup>19</sup> obtained cirrhosis in rabbits by keeping them for a long time in an atmosphere containing alcohol vapor. Joannovics<sup>20</sup> successfully repeated this experiment but Challand<sup>21</sup> and Magnan<sup>7</sup> were unable to do so. Saltykow<sup>22</sup> injected absolute alcohol in physiological salt solution in the ear vein of rabbits. One animal lived almost two years, receiving in this time eight injections, each containing 2½ c c of absolute alcohol. He found a resulting cirrhosis that was well marked macroscopically and microscopically.

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14 Strassman, F. Experimentell Untersuchungen zur Lehr vom chronischer alkoholismus, Vrtljschr f gerichtl Med, 1888, xlix.

15 Pupier, Z. Demonstration expérimentale de l'action des boissons dites spiritueuses sur le foie, Compt rend Acad d sc, 1872, p 1415.

16 Bischoff. Neue Beiträge zur experimentellen Alkoholforschung mit besonderer Berücksichtigung der Hertz und Leberveränderungen, Ztschr f exper Path u Therap, xi, Part 3, p 445.

17 Dujardin Beaumetz and Audige. Recherches expérimentales sur la puissance toxique des Alcools, Paris, 1879, Recherches expérimentales sur l'alcoolisme chronique, Paris, 1884.

18 Straus and Blocq. Etude expérimentale sur la cirrhose alcoolique de foie, Arch de physiol norm et path, 1887, Series 3, x, 409.

19 Mertens. Lésions anatomiques du foie du lapin au cours de l'intoxication chronique par le chloroforme et par l'alcool, Arch de pharmacod et de therap, 1896, ii.

20 Joannovics. Recherches expérimentales sur le pathogénie de l'ictère, Mém couron Acad roy de méd de Belg, 1903, Ueber Veränderungen der Leber bei Vergiftung mit Karbaminsäuren und kohlen Ammoniak, Arch de pharmacod, 1903, xii, Ueber experimentelle Lebercirrhose, Wein klin Wchnsch, 1904, xvii, 25.

21 Challand, T. Etude expérimentale et clinique sur absinthisme et l'alcoolisme. Thèse de Paris, 1871.

22 Saltykow, S. Beitrag zur Kenntnis der durch Alkohol hervorgerufenen Organveränderungen, Verhandl d deutsch Gesellsch, 1910, xiv, Experimentelle Forschung über die pathologische Anatomie des Alkoholismus chronicus, Zentralbl f allg Path u path Anat, 1911, xxii, No 19.

Fahr<sup>23</sup> repeated this work using 96 per cent alcohol on two rabbits and two guinea-pigs for a time period of two years and got a beginning cirrhosis in one rabbit. Lissauer<sup>24</sup> used 50 per cent alcohol and brandy in the ear vein of rabbits, and after seven months got evidence of cirrhosis. Schafr<sup>25</sup> reported success with similar experiments. Pogenpohl,<sup>26</sup> Siegenbeck von Heukelom,<sup>27</sup> Klopstock,<sup>28</sup> v Baumgarten<sup>4</sup> and Bischoff,<sup>16</sup> working along the same lines, got merely fat degeneration. Lancereaux<sup>29</sup> conducted experimental researches for years on cirrhosis of the liver, particularly the type that is seen in France, and as a result he concludes that alcoholic cirrhosis of the liver is the result of substances used in wine, beer, etc., for their preservation, especially potassium bisulphate. He was able to produce typical lesions of "gin-liver" by feeding animals this salt. The other salts of potassium gave negative results. Kyrle and Schopper<sup>30</sup> used a 50 per cent solution of absolute ethyl alcohol in equal parts of water and physiological salt solution intravenously, subcutaneously and by mouth on a series of thirty-one rabbits. The experiment extended over a period of from one hour to thirteen weeks. Each animal received alcohol every second to fourth day, in the dosage of 18 c c of absolute alcohol per kilo. In all cases the liver showed bile stasis, parenchymatous degeneration and fatty change in the liver cells. These changes commenced about the central veins. In seven cases there was necrosis of portions of the lobe and replacement fibrosis. In fourteen cases there was round cell infiltration of the interlobular spaces, and in seven others connective tissue proliferation with bile duct formation. The livers of three of the rabbits showed typical Laennec's cirrhosis. The authors state that degeneration only could be shown during the first two weeks of the experiment, but after that time the connective tissue reaction could be observed.

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23 Fahr. Zur Frage des chronischen Alkoholismus, Verhandl d deutsch path Gesellsch, 1909, xiii, Diskussionbemerkungen, ibid, 1910, xiv, ibid, 1911, xv, Virchows Arch f path Anat, 1911, ccv.

24 Lissauer. Lebercirrhose bei experimenteller Intoxication, Virchows Arch f path Anat, 1914, ccxvii, Part 1, p 56.

25 Schafr. Virchows Arch f path Anat, 1913.

26 Pogenpohl. Zur Frage der Veränderungen des Pankreas bei Lebercirrhose, Virchows Arch f path Anat, 1909, cxvi.

27 Van Heukelom Siegenback. Die experimentelle Cirrhosis hepatitis, Beitr z path Anat u z allg Path, 1896, xx.

28 Klopstock, F. Alkoholismus und Lebercirrhose, Virchows Arch f path Anat, 1906, clxxxiv, Zur Leber von der Lebercirrhose, Berl klin Wchnsch, 1910, Nos 33 and 34.

29 Lancereaux. Granular Cirrhosis of the Liver, Bull de l'Acad de med, Paris, 1910, lxxiv.

30 Kyrle and Schopper. Virchows Arch f path Anat, 1913, ccxv, Part 2, p 359.

In a previous communication I<sup>31</sup> made a preliminary report of work on experimental cirrhosis. Two of the cases reported were on experimental alcoholic cirrhosis and are as follows:

*Experiment 4*—A rabbit was given by mouth daily, except Sunday, before feeding-time in the morning, 15 cc of 34 per cent alcohol. This was given with a medicine dropper, and after a few administrations no difficulty was found in the rabbit's swallowing it. By this method I endeavored to reproduce as closely as possible the conditions in the steady drinker that are supposed to predispose to cirrhosis of the liver, namely, a repeated ingestion of alcohol in the "whisky proportion" on an empty stomach. This experiment was started Nov 4, 1912, and the animal killed April 9, 1913, covering a period of slightly over five months. Necropsy showed a liver small for an animal as large as this one (which at the beginning was a full sized rabbit, and which



Fig 1—Normal rabbit liver showing normal interlobular space with very slight amount of connective tissue between blood vessels and bile ducts

grew fatter and larger in the meantime, never showing any signs of being sick). The liver markings were extremely prominent and the organ was lighter in color and firmer, there was some slight roughening of the surface. Histologically, sections showed quite a large increase in the interlobular connective tissue in which there were many proliferating bile ducts, the buds and new branches of which stood out very distinctly. In several places it was evident that these were trying to penetrate the periphery of the lobules. The blood vessels were not particularly noticeable. The connective tissue seemed to be proliferating from the preexisting connective tissue in the interlobular

31 Grover, A. L. Experimental Cirrhosis of the Liver, Jour Am Med Assn, 1913, lxi, 458, The Question of Spontaneous Cirrhosis of the Liver in Rabbits and Other Laboratory Animals, Jour Am Med Assn, 1915, lxiv, 1487

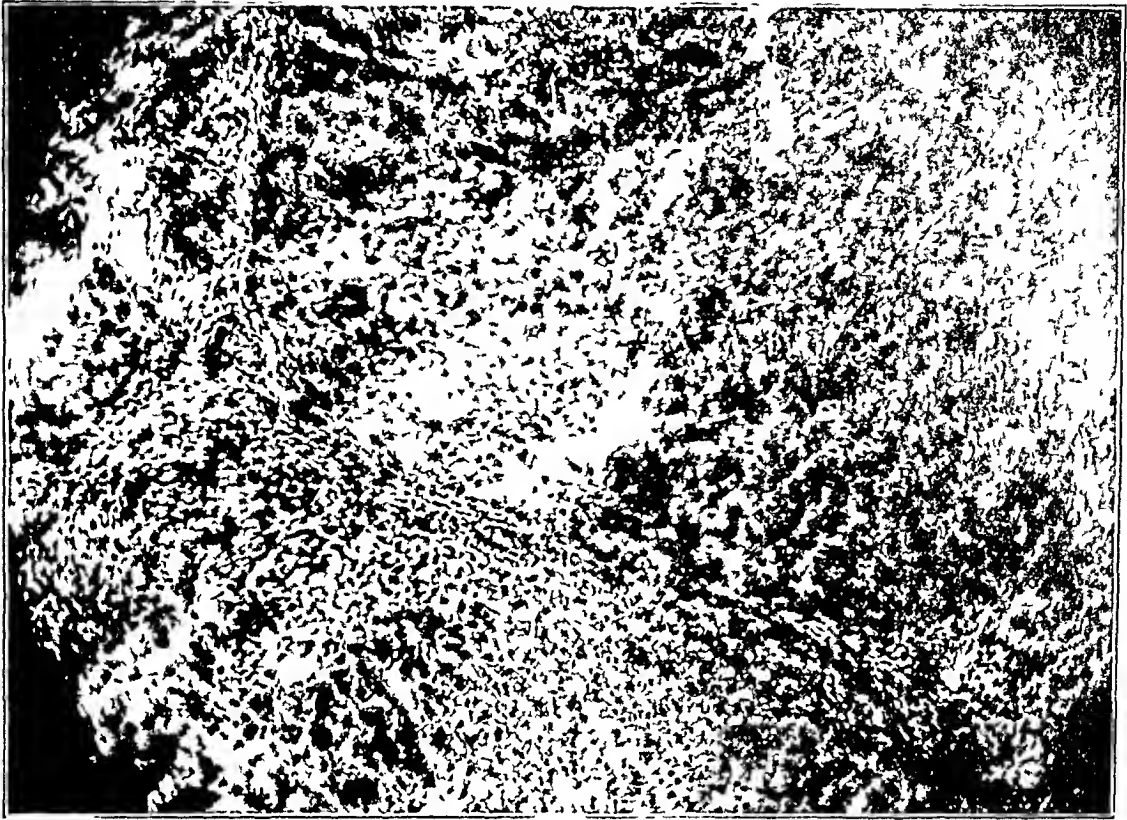


Fig 2—Showing a moderate cirrhosis (Animal 11) with areas of degeneration particularly at periphery of the lobule

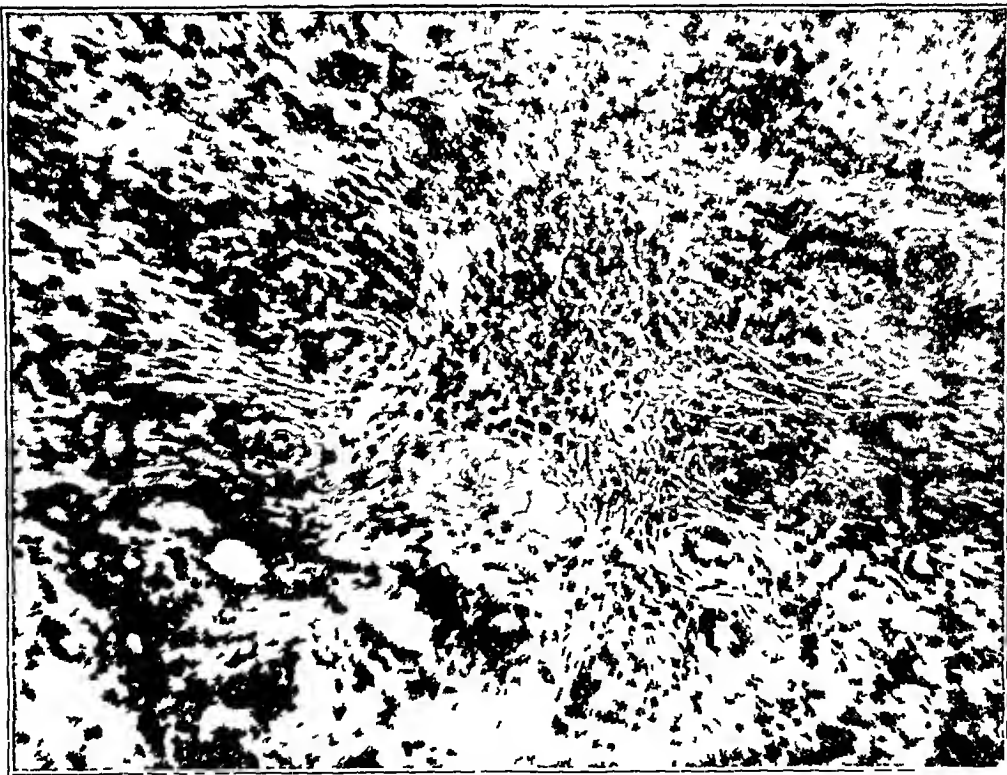


Fig 3—Marked cirrhosis (Animal 7), shows dense proliferation of connective tissue in interlobular spaces with many new formed bile ducts

spaces. Some ingrowth into the lobule had taken place, but was not particularly far advanced. More or less increase of the intralobular connective tissue was also observed. The cells of the liver parenchyma showed pretty much throughout a moderate degree of albuminoid degeneration. Occasionally the central part of the lobule and in one place a whole lobule had undergone a more severe change, but not far enough to be called a true necrosis. With the higher power of the microscope the protoplasm of the cells has the lattice-work arrangement of threads as described previously. These threads where they crossed one another seemed to be sort of bunched up in a way similar to the nodal points in fibrin fibers. The protoplasm of the cells had a tendency to gather at the periphery of the cell along the cell membrane, and these threads intervened across the more central portion. The nuclei stained rather irregularly, having somewhat of a similar thread-like appearance of its chromatin. Karyokinetic figures were rarely observed, but a good many cells were seen

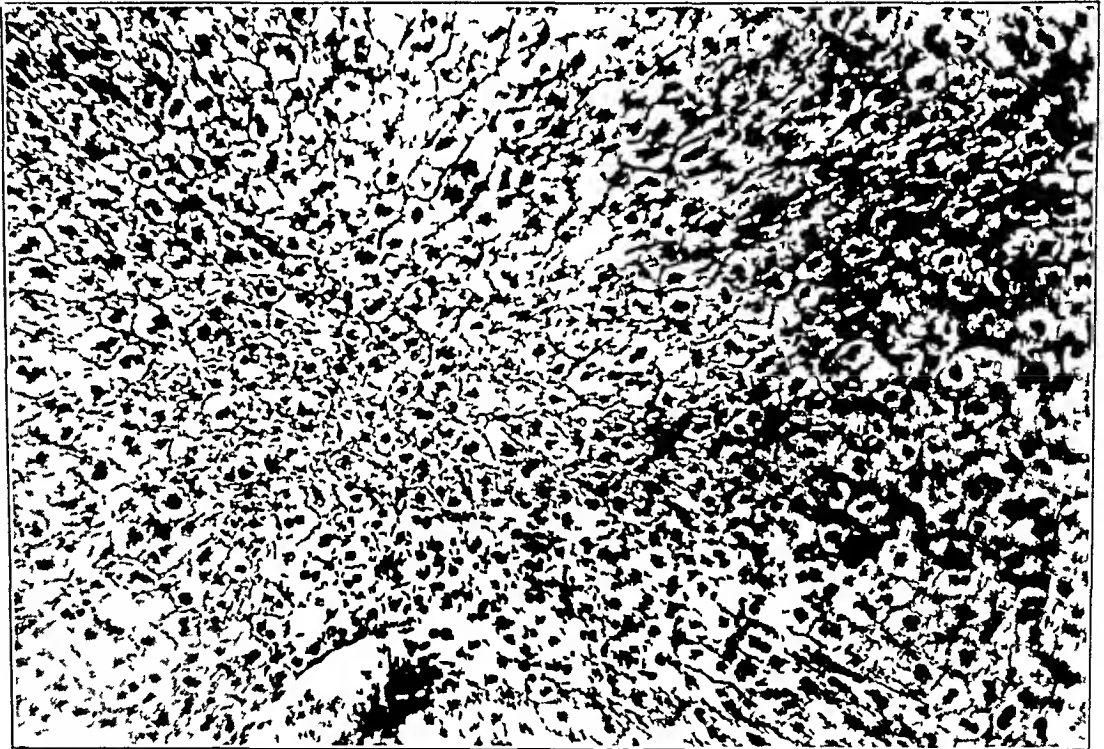


Fig 4—Complete parenchymatous degeneration with vacuolation (Animal 12). Nuclei appear broken up or have entirely disappeared.

with double nuclei. In some cells the nucleus was apparently lost, yet the protoplasm had the characteristic appearance already noted. An occasional cell was vacuolated, but nothing could be determined as to the contents of the same. Once in awhile a cell or a group of cells would stain more brightly than the others. As some of these had double nuclei, I took them to be regenerated or regenerating cells. Very rarely in the protoplasm of a cell could be made out a portion, really one of these nodal masses mentioned before, that took a brighter stain with eosin than the others. This may be the beginning of that hyaline skein-like degeneration that Mallory believes to be pathognomonic of alcoholic cirrhosis.

The intralobular blood capillaries were dilated and their walls could be fairly well made out. The endothelium of these as well as that of the lymph spaces in the portal regions was actively proliferating.



*Experiment 5*—Another animal was treated in the same way for four months, but at the end of the third month was inoculated with 0.5 cc of a bouillon culture of *B. coli* in the ear vein. Histologically the liver shows a beginning of cirrhosis but much less than the last. The bile ducts have not yet undergone any change, thus showing that bile-duct proliferation is a later process than the proliferation of connective tissue. The colon bacilli seemed to have no influence, thus acting contrary to the results obtained with it in chloroform necrosis.

Since this report was made another series of experiments have been carried out all on rabbits. In all, twelve animals have been fed alcohol in same dosage as in the first experiment. Six other rabbits, four from same litters and two from other litters, have been saved for controls. In brief these experiments resulted as follows:

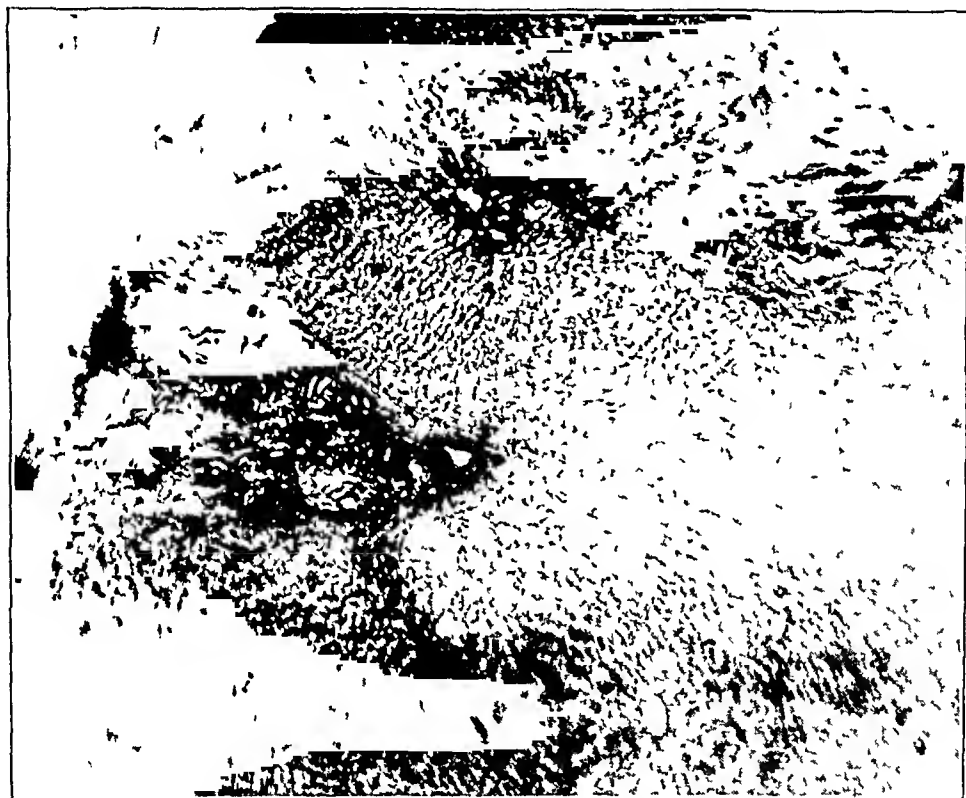


Fig. 5—Extensive cirrhosis (Experiment 4), the interlobular connective tissue proliferation is well marked, but new formation of bile ducts is the most prominent feature.

*Animal 1*—Lived eight months. Liver shows no gross changes but microscopically one sees areas of degeneration, particularly in the periphery of the lobules, but in some areas extending in as far as the central vein. In one or two lobules there seems to be complete necrosis of cell protoplasm with vacuolation. The interlobular spaces are filled with proliferated connective tissue, which is commencing to invade the periphery of the lobules.

*Animal 2*—Lived five months. Examination of liver showed passive congestion with some central necrosis. All the trabeculae seemed to be widely separated. There is some slight connective tissue increase in the interlobular spaces.

*Animal 3*—Lived four months. Liver showed nothing except some fatty degeneration.



*Animal 4*—Lived three weeks Liver showed no change

*Animals 5 and 6* were controls One lived nearly a year and then died from pneumonia Liver showed no lesions The second control is still living after thirteen months

*Animal 7* lived about ten months Shows a marked cirrhosis

The interlobular spaces throughout show very marked proliferation of connective tissue which is crowding in on the lobules, very profusely invading the parenchyma cells, which are more or less degenerated

*Animal 8* lived eight months Showed a moderate degree of cirrhotic changes about half way between that of *Animals 1* and *7*

*Animal 9*—Control Lived eleven months and then was killed by a dog that broke into the pen Showed no liver lesions

*Animal 10*—Lived six months, showed marked beginning cirrhosis

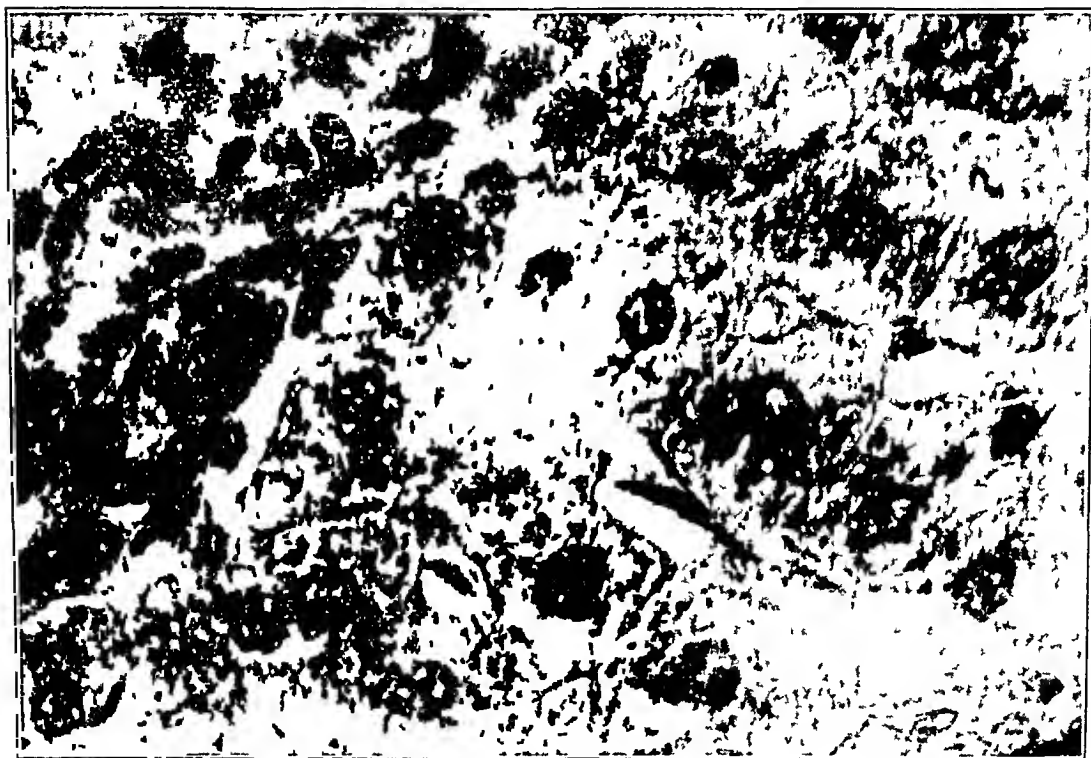


Fig 6—High power of liver parenchyma from same slide as Figure 5 Shows the skein-like formation of protoplasm with masses undergoing hyaline degeneration

*Animal 11*—Lived nine months, showed considerable connective tissue reaction A rather marked cirrhosis with considerable bile duct proliferation A good deal of parenchymatous tissue seems to have disappeared and to have been replaced by connective tissue The newly-formed bile ducts can be seen running in the midst of this dense fibrous tissue

*Animal 12*—Animal killed after about twelve months on account of a severe long-standing torticollis After nine months, the dose of alcohol was doubled After two months more it was again doubled Necropsy showed a pale, soft, enlarged liver Microscopically, the cells are completely degenerated Nothing remains but a vacuolated cell with a broken up nucleus In many instances the nucleus had disappeared

*Animal 13*—Lived ten months Had to be killed, as overgrowth of lower teeth resulting from broken upper ones prevented animal from eating Liver

showed enormously enlarged blood vessels and capillaries and quite a marked cirrhosis that appeared to be originating entirely from the blood vessels and in many places it was somewhat of the nature of an adventitial sclerosis

The rest of the animals and controls are still alive. It is interesting to note that almost all the young born of females treated with alcohol were killed by the mother while those from the controls lived. From the work of previous writers, as well as from this work, it appears that the cirrhotic change is entirely a reparative process stimulated by injury to the liver cells. The injury of the cell is manifested by albuminoid and fatty degeneration, but also particularly by vacuolation. At the same time there seems to be a gathering of the protoplasm into the skein formation previously mentioned, where it appears to be

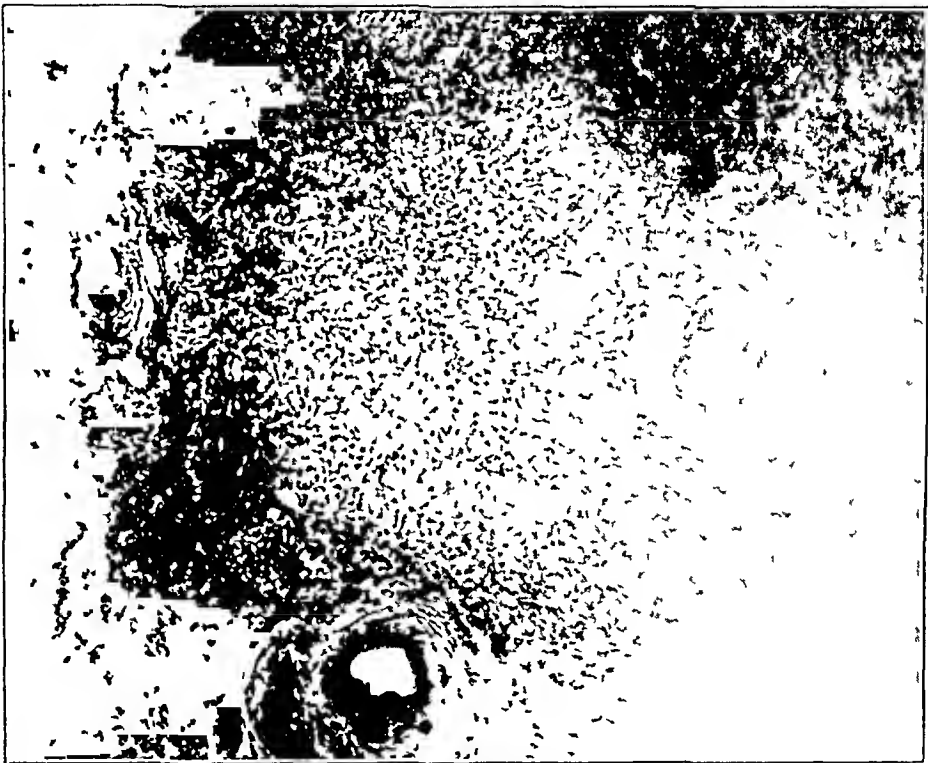


Fig 7—Showing a very early cirrhosis. The new formed connective tissue is seen proliferating from the region of bile ducts. Animal 10

taking on a hyaline appearance very much like that which Mallory mentions as the diagnostic sign of alcohol degeneration. In all cases active regeneration of liver cells can be observed.

Some observers have claimed that spontaneous cirrhosis of the liver is a common condition in rabbits. This question has been fully considered in a previous contribution<sup>31</sup>. The evidence presented in this contribution was briefly as follows:

Nearly three hundred rabbits had been necropsied as a routine laboratory procedure, and these were used as controls for the foregoing experiments with alcohol. No evidence of cirrhosis of the liver was found except in one case, in which the common bile duct was

experimentally ligated, in one case of experimental pyemia, in one case of experimental chloroform intoxication, in three cases in which the rabbits died as a result of spontaneous pyogenic infection, and finally, in one case of infection with *Coccidia oviforme*. These animals were of the same strains as the ones used in the alcohol experiments together with many other strains, thus giving as fair a control as would be possible for one to find. As a result there has been no evidence found of spontaneous cirrhosis of the liver. The evidence brought forward by others is of interest, but I believe that a more careful examination would have shown evidence of infection of some sort as the source of the connective tissue proliferation.

In conclusion, it seems that when alcohol is given for a long period there follows degeneration of the liver cells, which in a large proportion of cases is followed by connective tissue proliferation. Whether any other process comes in to help is uncertain, nevertheless it remains pretty well proved that a cirrhosis can be obtained from alcohol in cases in which no other factor is apparent.

# THE BLOOD AND THE BLOOD VESSELS IN HEMOPHILIA AND OTHER HEMORRHAGIC DISEASES <sup>\*</sup>

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It is becoming increasingly evident that the group termed "the hemorrhagic diseases" includes a large number of abnormal conditions, and that, at the present time, it is a fruitless task to attempt to unravel the various entities embraced by the clinical conditions which are assembled under this general head. This is due partly to the fact that the physiology of the coagulation of the blood is still incompletely understood, partly because of the impossibility of analyzing the various factors concerned in coagulation, and in part because these hemorrhagic states have been incompletely observed from a clinical point of view. Indeed, the knowledge and the methods which are at our disposal have by no means been fully and intensively applied to solving the problems which these cases present.

There are two hemorrhagic states which stand out in relief—true hemophilia of the hereditary type, found almost exclusively in males and transmitted through the female, and on the other hand, the purpuric conditions, embracing many varieties and found quite as frequently among females as among males. Under this latter heading are included purpura hemorrhagica, Henoch's purpura, simple purpura, the purpura of the new-born, and many other forms which have received more or less wide recognition. It would evidently be impossible to attempt to consider these multitudinous disorders, and, we may add, would be to no purpose and lead to no definite conclusions. A brief consideration of the clinical manifestations which are supposed to distinguish these conditions one from the other is convincing that sharp boundary lines do not really exist and that at present no satisfactory differentiation can be drawn. We shall therefore consider purpura rather as an entity and compare it to hemophilia. Miss Mildred Fish has assisted in a large part of this investigation.

During the past year or more we have had the opportunity of studying the blood and observing clinically several cases of typical hemophilia, as well as some atypical instances of this disorder, and numerous cases of purpura. The opportunity has been unusual in that many of the children have been inmates of the Hebrew Infant

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Asylum, which rendered it possible to watch them clinically for a long and continuous period, and to carry out a large number of examinations of their blood. These tests included as a routine the determination of the coagulation time and of the amount of antithrombin present. In testing the coagulation of the blood and plasma, Howell's method<sup>1</sup> was followed. For the plasma, this consists of mixing the blood, which is obtained directly from the vein, with 10 per cent of a 1 per cent sodium oxalate solution. This mixture is centrifugalized for fifteen minutes and the supernatant plasma is pipetted off and recalcified with varying amounts of a weak calcium solution. In addition, frequent counts of the blood platelets were made by means of the Wright and Kinnicutt method, and many tests which will be referred to in the body of the paper.

TABLE 1—VARIATIONS IN COAGULATION OF NORMAL PLASMA (A F H)

Date	Coagulation Time minutes	Remarks
1914 March 24	3	Antithrombin test (Howell) showed a deficiency of this substance
April 28	8	Coagulation time of blood six minutes
April 30	4	
May 26	4	
June 15	10	
June 19	12	Coagulation time of blood September 3 was six and one-half minutes
Aug 26	8	
Sept 11	11	
Oct 21	10	

The pathogenesis of true hemophilia is still obscure. Some, following Howell, believe that the defect lies in an insufficiency of prothrombin in the blood, others, following Morawitz, attribute the excessive bleeding to a lack of thrombokinase. There is, however, concordance in the belief that the main defect lies not in the blood vessels, but in the blood itself. Normal plasma tested after the manner just described, forms a firm clot in about ten minutes (Table 1). The plasma of the hemophiliac has a delayed clotting time, varying generally from about one-half hour to many hours. The accompanying table (Table 2) shows numerous tests of plasma in several cases of hemophilia in patients who gave a classical hereditary history.

The first two are brothers (Hyman and Julius S.). There is one other child in the family, a girl of about 12 years. She is perfectly well and had her tonsils removed without hemorrhage. The father's family history is negative.

1 Howell, W. H. THE ARCHIVES INT. MED., 1914, XIII, 76

TABLE 2—COAGULATION TIME IN HEREDITARY HEMOPHILIA CASES  
A HYMAN S (5 YEARS OLD)

Date	Coagulation Time Plasma minutes	Coagulation Time Blood minutes	Remarks
1914			
March 11	25		Platelets 197 000
March 20	10		
March 24	15		
April 21			Did not clot
May 26	24		Bleeding from tongue April 25 to May 2
June 1	20	22	
June 8	20		
June 26	10		No loss of blood, hemarthrosis of knee
Sept 16	16	13	
1915			
June 12	8		Severe hemorrhage of tongue stopped by thromboplastin
June 19	12		

B JULIUS S (9 YEARS OLD)

1914			
May 5	36	61	Hemarthrosis of ankle
May 26	16		Platelets, 300,000, leukocytes, 17,000
Aug 26	19		In hospital, bled five days after incisor tooth extraction
Sept 14	42		
Nov 24		35	
Dec 11		34	
Dec 14		60	
Dec 16		20	Bleeding from finger all day
Dec 17		34	
Dec 21		48	

C WM B (7 YEARS OLD)

1914			
Nov 13	52	90	Plasma of brother (9 years old) clotted in nine minutes
Nov 20	20	55	
Nov 24		106	
Dec 16	100	210	Five days ago severe bleeding from tongue
1915			
June 14	24		Plasma of brother (20 years old) clotted in twenty-six minutes

The mother had no tendency to bleeding and had a peritonsillar abscess opened without great loss of blood. Her two sisters' children are also bleeders. One sister lost two boys from hemorrhage, one of these died following an injury to the mouth which broke several teeth, the history of the other is not definite. Another child (a girl) is supposed to bleed severely from cuts, so that a physician has frequently to be called. Another sister (an aunt of Hyman and Julius) has a daughter (Yetta K.) who is a bleeder and who will be discussed at greater length. As for the boys themselves, they have been in the Hebrew Infant Asylum for a number of years, have had frequent hemorrhages into the joints (ankle, knee, vertebrae), have bled from the tongue several times so as to necessitate their removal to a hospital, and are at no time free from large "black and blue" marks. Julius had to be taken to a hospital when ten days old, on account of hemorrhage following circumcision. At 2½ years of age he was transfused at a hospital on account of loss of blood.

Wm. B. is an Italian with a classical history. He is one of twelve children, the girls are normal, one boy died of hemorrhage, another is absolutely free from this tendency and has a normal coagulation time, a third is a bleeder and as a result is crippled with stiffening of the elbow and knee joints. The maternal uncle of the boy died at the age of 18 of hemorrhage. There are two maternal aunts, one had eight sons, seven of whom were hemophiliacs, the other had five sons, of whom four were hemophiliacs.

A glance at the column (Table 2) giving the clotting time of the plasma shows that, compared to the normal, it was almost regularly delayed. The first two cases, the brothers Hyman S. and Julius S., must be considered rather mild examples of hemophilia, in spite of the fact that at all times they manifested subcutaneous hemorrhage, and from time to time suffered from prolonged and serious hemorrhage.<sup>2</sup> The variability in coagulation time, which is a striking feature, has been found by various investigators to be the rule rather than the exception in hemophilia, although the cause of these variations has never been explained. The two tests of Hyman S., March 20 and January 26, are particularly interesting and noteworthy, because the coagulation time was only ten minutes, that is, was well within normal limits. This rapid clotting was not occasioned by previous hemorrhage (a phenomenon first noted by Sahli), nor by an admixture of tissue juice. These tests mean that had we depended on the clotting time of the blood on these two occasions for a diagnosis of the nature of the hemorrhagic condition, we should not have regarded the case as one of hemophilia. It emphasizes the necessity of numerous coagulation tests in every case. In spite of these occasional variations, the fact holds true that a marked delay in the coagulation of the blood is the most characteristic sign of hemophilia.

Another important element in diagnosis is the number of blood platelets. Our experience confirmed that of Duke<sup>3</sup> and others, that

2 The elder of these boys bled for several days following an injury to his tongue, and is the case referred to in an article on "Tissue Extract as a Hemostatic," where the local application of thromboplastin brought about almost instantaneous clotting. (*Jour. Am. Med. Assn.*, 1915, *lxiv*, 1395.)

3 Duke, W. W. *THE ARCHIVES INT. MED.*, 1912, *x*, 445.

in hemophilia the platelet count is normal, whereas in purpura it is low, frequently less than 100,000. In our cases of hemophilia the platelets never fell below 320,000 per cmm, and in some tests numbered over 500,000. In purpura, on the other hand, the counts never exceeded 200,000. These cells have recently been the object of particular attention, as they contain a considerable amount of thromboplastic substance, the thrombokinese of Morawitz, and it seemed as if their study might shed new light on the pathogenesis of hemorrhagic conditions. Examinations of many cases have convinced us that the microscopic appearance of platelets is not always the same, that from a morphologic standpoint we can in some instances differentiate and distinguish between them. In one case of marked purpura, on which we carried out many platelet counts and numerous other tests, the platelets, on two occasions, were exceptionally large. In another instance the platelets were unusually small, appearing almost fragmented. It is probable that in future it will be well to note these *macro- and micro-platelets*, just as we are accustomed to take cognizance of the macrocytes and microcytes among the other blood cells.

Following puncture of the skin by a hypodermic needle, we should expect in hemophilia an exaggerated degree of bleeding, at least a small areola of hemorrhage, about the puncture wound. Such, however, is not the case. In one of our cases (H. S.), who developed diphtheria, numerous subcutaneous injections of antitoxin were given and not only did these inoculations not result in any marked hemorrhage, but there was not the slightest extravasation at the site of the injection. This circumstance and the fact that we can carry out venepuncture with impunity, is probably attributable to the thromboplastic activity of the tissue juices which continue to exert their complementary coagulative function in this disorder.<sup>4</sup>

This lack of hemorrhage following a puncture of the skin is sufficiently constant to be accorded some diagnostic significance, especially as quite the contrary reaction is occasioned in purpura, a marked hemorrhagic area manifesting itself at the site of puncture.

As has been shown by Duke,<sup>3</sup> the bleeding time is increased in purpura. By this is meant that bleeding does not stop as promptly as in the normal individual, but that the blood wells forth drop by drop for a considerable period. The test is extremely simple, a prick is made with a needle into the lobe of the ear and the drops of blood

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4 The accompanying illustration shows a remarkable clot which formed on the tongue of a hemophiliac (Julius S.) at the site of hemorrhage. The clot was evidently held firm at its rim by the complementary action of the tissue juice, whereas the hemorrhage continued to some degree in the center. As a result, a cylindrical clot, fully one-half inch in length, developed. This clot, which resembled a papilloma, checked the bleeding for some days.



are absorbed with blotting paper. If the blood oozes for more than three minutes, the bleeding-time is considered increased. The test is of value in a positive sense, namely, if the time is found to be prolonged. The results vary considerably even from apparently identical punctures made at the same time. In hemophilia, the bleeding-time is generally normal. That this is so can be attributed probably to the same complementary factor as the normal "puncture test."

Some time ago we described a test, termed the "*capillary resistance test*,"<sup>5</sup> which is carried out as follows. A tourniquet is applied to the upper arm sufficiently tight to obstruct the venous flow, but not to completely obliterate the radial pulse. In infants, on whom this test was extensively carried out, pressure of about 100 mm of mercury is required for the purpose. This pressure is maintained for three minutes, during which period, if it is properly applied, the forearm should become markedly cyanosed. The tourniquet is then removed



Blood clot following hemorrhage of tongue in hemophiliac

and we note whether a large number of petechiae or small hemorrhagic spots have developed on the forearm. This test has been found useful in differentiating between purpura and hemophilia. It is surprising the degree of pressure which the blood vessels withstand in hemophilia without the formation of minute hemorrhages. In purpura, on the other hand, as must have been noticed by those who have applied a tourniquet in the course of aspirating blood, the application of the tourniquet quickly brings about not only petechiae, but even larger subcutaneous hemorrhages.

Let us turn now to hemophilia. It is common knowledge that this disorder has shown itself to be of most marked hereditary character, and that this heredity is peculiarly sex-linked, being transmitted by the female and manifested by the male. This law of heredity, which is sometimes termed the law of Nasse, runs so true that many have

<sup>5</sup> Hess, A. F., and Fish, Mildred. *Am Jour Dis Child*, 1914, viii, 386

believed that it is without exemption, and have cast aside as unconvincing or unauthentic all cases which seem to run contrary to it. Let us consider this question, but, first of all, the simple one of hereditary bleeders.

The striking hereditary character of true hemophilia has frequently led to the assumption that the mere fact that the bleeding tendency was hereditary constituted strong evidence for the hemophiliac and against the purpuric nature of the disorder. This has been our experience in regard to cases referred to us by physicians, and is the point of view which pervades the literature of the hemorrhagic diseases. The matter, however, is not so clear cut. The fact is that, although purpura may not be hereditary, and may be idiopathic or due to sepsis or many other causes, there is a definite *hereditary purpura*. Whether this form of purpura differs from other forms in respects other than that it is not acquired, we are unable to state, but the hereditary nature of the bleeding seems no more open to question than the heredity of true hemophilia. Such being the case, it would seem advisable, from a clinical standpoint, to recognize and to emphasize this fact, and to make a tentative grouping of these cases under the title of hereditary purpura. The following are cases of this description.

1 Edward G, 11 years old, suffers from frequent nose bleed, bleeds markedly from cuts, has bled for days following extraction of a tooth, and has numerous "black and blue" marks on his body. He is one of eleven children, ten of whom were boys. The girl is alive and well and normal. Six of the children have died and three of them were bleeders, one died of hemorrhage from the cord when a day old, another when  $2\frac{1}{2}$  years old, and a third when 17 years old. Of the four boys who are alive, only this one shows evidence of being a bleeder. The father has given evidences of bleeding inordinately since he was 8 years old, he has suffered from frequent nose bleed all his life, has been in a precarious condition following the extraction of his teeth, and frequently has ecchymoses into the skin. His father and mother died at the age of 75 and 84, respectively, and were never troubled with bleeding. His wife and her parents were normal.

This case was diagnosed as true purpura from the fact that the platelets numbered only 62,500, that the plasma coagulated in eight minutes, and the bleeding time was increased. We may add that this case showed macroplatelets.

2 Morris G,  $6\frac{1}{2}$  years old, bled after circumcision to such a degree that an operation was necessary. When  $2\frac{1}{2}$  years old he fell and bled from the frenum of the lip, requiring the services of a physician. About two years ago a front tooth was pulled and he bled for three or four days and lost considerable blood. Recently he fell and again bled from his lip, after many styptics were applied, the hemorrhage was checked by the physician applying some of his own blood.

There are seven children in this family, five girls and two boys. The only other child who shows a hemorrhagic tendency is the boy, who is 9 years of age, and bled alarmingly when circumcised, and when a tooth was pulled. On this latter occasion he bled for five days and many physicians were called to

see him. He also has frequent nose bleed. The father of the boy gives a history of marked bleeding following circumcision, of frequent nose bleed and of excessive bleeding following cuts. He has a brother and a sister who are well. His wife is perfectly healthy and has three brothers living in this city who do not bleed, her mother and father also had no trouble.

The plasma of this boy coagulated in ten minutes on November 4 and December 2. His platelet count was 98,000 and bleeding time increased.

The following case, which was kindly referred to me by Professor Howell of Baltimore, is striking both in regard to its definite hereditary character and its clear cut purpuric nature. It was observed closely for many months. The following is a summary of the history, which was obtained in detail from Dr. A. E. Fendrich of Weehawken, N. J., who had treated the girl for many years.

Lilian P., 18 years of age, frequent nose bleed and purpuric spots since the age of 12. Menstruation began at 14 and assumed the character of profuse hemorrhage, so that the girl became comatose and was transfused (the mother acting as donor). Seven months later she developed gangrene of one of her fingers, which had to be amputated. Nose bleeding was frequent and ecchymoses into the skin were present. Somewhat over a year ago there was a hemorrhage into the ankle joint. Menstruation was always profuse and last winter twice threatened life, so that transfusion was performed.

Her father had frequent nose bleed and his family were known as nose bleeders, one of his brothers suffers from nose bleed, one sister died of apoplexy at the age of 45. Her mother always suffered from "blue spots," as did many members of her family, the mother's sister was known to her physician as a "bleeding woman," and has five children who all bleed from the nose frequently, the mother's brother died suddenly, at the age of 35, of heart disease.

Lilian has a brother who bled for two or three days a year ago following the extraction of a tooth, another who has frequent nose bleed, a third who frequently has "black and blue" spots, she has two sisters, one is normal and the other has a nevus extending over her right forearm and hand.

The plasma of this girl coagulated in six to ten minutes in tests made frequently from November to March. Her platelet count was almost always below 100,000, ranging between 80,000 and 90,000. Her bleeding time was increased, her capillary resistance tests markedly positive, her puncture test also positive. This was one of the cases referred to above, where, on occasions, microplatelets were noted, and small, shrunken or fragmented platelets.

This case seems of interest from many aspects. There can be no doubt of the hereditary nature of this purpura. Cases of this description are generally considered hemophilia, and if the heredity points to the father, they may be reported as rare instances of hemophilia inherited from the male. There are one or two other circumstances which should be noted in connection with this history. It will be observed that on one occasion the girl had a hemorrhage into the ankle joint. This is a lesion which is generally regarded as being distinctive of hemophilia. Furthermore, we cannot but be impressed by the num-

bel of disorders in this family which are due, at least in part, to vascular defects, the apoplexy of the aunt at the age of 45, the large nevus of the arm of the sister, the gangrene of the finger of the patient, and perhaps the sudden death of an uncle at the age of 35. As the vessels are probably involved in purpura, these incidents in the family history assume increased significance <sup>6</sup>

In almost all studies of hemophilia, particular emphasis has been laid on its striking incidence—the fact that it occurs solely in the male and that it is invariably hereditary in origin. Although we have not encountered any case which absolutely controverts these premises, it seems inadvisable and unwarranted to establish such hard and fast limitations as have been set down in the comprehensive monograph on hemophilia recently issued by the Eugenics Laboratory <sup>7</sup>. The literature of the subject cannot be used to decide this question, as it is most difficult to pass on the reported cases, to accept some and to reject others as hemophilia, for conclusive evidence is lacking. For example, there are comparatively few cases cited in this monograph in which a coagulation test of blood, obtained directly from a vessel, has been made, or where a count of the blood platelets is reported. We therefore have to rely solely on the clinical manifestations and, as has been seen from the case (Lillian P.) just reported, these phenomena may be insufficient in themselves to permit of a differential diagnosis. In this connection it should be borne in mind that in other diseases confined to the male sex, diseases which have the advantage of being susceptible to more ready diagnosis, such as color blindness and pseudo-muscular dystrophy, well authenticated cases have been described in the female. We raise this question, as we have met with two instances in which a hemorrhagic condition assumed a hemophiliac type in the male, and a purpuric type in the female member of a family. The one case is Yetta K. who is a cousin of Hyman S. and Julius S., whose histories have been recorded above. The coagulation time of the blood of these boys, together with other data, may be seen in Table 2. We may summarize their cases by stating that they have been under observation for some years and that, according to all the diagnostic signs which we have enumerated above, they have classical hemophilia.

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6 In purpura there is a tendency to multiple hemorrhages as shown by the great number of petechiae, there is also a hemostatic defect, which is probably associated with the lack of platelets. In hemophilia there is no tendency to frequent hemorrhages, and probably bleeding does not occur more often than normal, there is merely the tendency to excessive bleeding, due to defective blood coagulation.

7 Bulloch and Fildes. Hemophilia, Eugenic Lab. Memoirs, Univ. of London, 1911, xii.

Yetta is their cousin by a maternal aunt, is 18 years of age and well, except for the fact that she suffers from bleeding, which interferes with her work. Since 8 years of age, she has had epistaxis, which has occurred almost daily for the past year. Last year she bled for some weeks following the extraction of a tooth. She also suffers from menorrhagia. Physical examination merely showed that she had numerous ecchymotic marks on her arms and legs. Her plasma coagulated in six minutes, the capillary resistance and puncture tests were markedly positive. The blood platelets were 155,000.

In other words, from a clinical and from a laboratory standpoint, her condition must be diagnosed as purpura rather than hemophilia.

The other instance of this peculiar clinical differentiation according to sex is more interesting, as it involves a sister and brother.

The children were admitted to the Hebrew Infant Asylum last spring. The girl (Millic W.) was almost 4 years old, and the boy 1 year of age. An indefinite and unsatisfactory family history was obtained. Both appeared well when they entered the asylum. Soon afterward, however, both manifested signs of bleeding. The girl bled from the nose and from the bowel and showed a profuse hemorrhagic eruption of the skin, with large ecchymotic spots, as well as numerous pin point hemorrhages, which preponderated on the extremities. The mucous membranes of the mouth and of the vagina, as well as the conjunctivae, were peppered with petechiae. There was oozing from the tip of the tongue. The capillary resistance test was markedly positive, puncture of the skin resulted in a large subcutaneous hemorrhage, the bleeding time was greatly prolonged. The plasma clotted in thirteen minutes on June 25, and in twenty minutes on the following day, and seemed slightly hemolyzed. The platelets numbered 76,000.

The conditions in the boy, who was 1 year old, were quite different. He gave a history of having bled for ten days following circumcision. He was somewhat pale, although not markedly anemic looking. Hemoglobin 63 per cent, red blood cells, 4,800,000, weight, 17½ pounds. The appearance of the hemorrhagic skin lesions was totally different from that of the girl.

There were only two subcutaneous hemorrhages, an ecchymosis over the knee and another over the forehead, and an absence of small petechiae. The bleeding time was slightly prolonged, the puncture test and the capillary resistance test absolutely negative. The blood platelets numbered 351,000 on one occasion, 400,000 on another. The plasma coagulated once in twenty-one minutes and in thirty minutes on the following day. There was no bleeding from the bowels. Pain, and possibly hemorrhage, was present in the knee joint.

Here then are two contrasting pictures. The girl with purpura typical in all respects, corresponding in its various clinical and laboratory aspects to the description which has been sketched above, the boy showing a quite different symptomatology, corresponding to hemophilia. The basis of this difference is entirely obscure, although it is possible to suggest attractive hypotheses. Similar cases should be looked for in the future, and the possible bearing of sex on the manifestations of other diseases, particularly blood diseases, should be borne in mind.

Although it is advisable to regard true hemophilia as a clearly defined entity, and to sharply contrast it with purpura, both of these

disorders probably embrace various types of disease Recently we described a case<sup>8</sup> of hemophilia which had been under observation for a long period and was exceptional in having a deficiency of calcium in

TABLE 3—COAGULATION TIME OF CALCIPRIVA CASE

Date	Coagulation Time Plasma minutes	Coagulation Time Blood minutes	Remarks
1914			
April 21	58	29	Control plasma clotted in eight minutes, capillary resistance test negative
May 21	16	11½	Frontal hematoma, nose bleed Platelets 487,000 Antithrombin normal in first test, increased in this test compared with controls Platelets 367,000
May 23	30		
May 26	28		
May 28	28		
June 15	22		Has many "black and blue" marks
June 25	18		
Aug 19	12	10	<i>Has been bleeding</i> from finger for some days The addition of calcium did not hasten coagulation of the blood The plasma clotted in optimal time in the tube with only two drops of calcium solution added
Aug 24	12		Antithrombin not increased Has hemarthrosis of hip
Oct 24		15	Blood clotted in eight minutes on addition of Ca
		15	Blood clotted in eight minutes on addition of Ca, whereas control blood was delayed
Nov 10	32	15	Has had nose bleed twice two days ago Has received calcium lactate for four days The addition of calcium did not hasten coagulation
Nov 17	34		
Dec 2	12	7	<i>Has been receiving calcium lactate for some weeks</i> Calcium delayed clotting time when added to the blood Has not bled for some time Looks well
Dec 28	34	12	
Dec 29		40	Calcium did not hasten coagulation
1915			
June 26	88		
July 2	60		
July 9		34	Addition of calcium made clotting time thirteen minutes
Sept 8	22		

the blood As is well known, although in the early studies of hemophilia attention was directed to the calcium factor, it was shown by

Nolf and others that calcium was present in normal amount in the blood, and by Morawitz and Lossen that an addition of lime salt does not hasten coagulation We shall not repeat the details of this case which, as far as we know, is unique, but have summarized some of the data in Tables 3 and 4, and may add that the addition of a small

TABLE 4—EFFECT ON CLOTTING TIME OF ADDITION OF CALCIUM SOLUTION TO BLOOD

A NORMAL CASE					
Clotting Time minutes	Control	Drops of Ca Solution Added			
		1	2	3	4
4	+		+	+	+
5	++		++	++	++
6	+++*		+++	+++	+++
7				+++	+++
9				+++	+++
11				+++	+++
13				+++	+++
15				+++	+++
17				+++	+++

B HEMOPHILIA CALCIPRIVA					
5	—	—	—	—	—
9	—	—	—	—	—
11	—	+	++	—	—
13	—	+	+++	+	—
17	—	+++		++	+
21	—			+++	++
26	+			+++	+++
34	+++				+++

C TYPICAL HEMOPHILIA					
4	—	—	—	—	—
8	+	++	+	++	+
10	++	++	++	++	++
14	+++	+++	+++	+++	+++
18		+++	+++	+++	+++
22		+++	+++	+++	+++
26		+++	+++	+++	+++
30			+++	+++	+++

\* + + + denotes complete clotting

amount of a weak calcium solution did hasten coagulation, that a sub-normal amount of calcium was found by analysis in the blood, that a metabolism test showed a negative balance for calcium, which became positive when lime was added to the diet, whereas a control metabolism test of a typical hemophiliac (Julius S) was normal in all respects

These chemical tests were carried out by Dr Max Kahn. We have here then an atypical hemophilia, a hemophilia calcipriva. Probably similar cases will be found, and other instances of hemophilia differing in one factor or another from the classical model, will be encountered from time to time.

Purpura is far less well defined than hemophilia. From a clinical point of view, it would seem advisable for the present to have purpura include all bleeders who show a deficiency of blood platelets. These cases will manifest many or most of the signs which have been discussed at the beginning of this paper. It is realized that a grouping which rests on such a basis may have no unity from an etiologic standpoint and merely be tentative in nature. It furnishes, however, that which does not exist at present, a definite criterion, namely platelet deficiency, just as retarded coagulation of the blood is regarded as the essential diagnostic factor in hemophilia. Most cases of purpura conform to this standard. Not all, however. There are cases which cannot be classified because they manifest the characteristic signs of both purpura and hemophilia. To illustrate

Jessie K., a girl of 4 years, seen with Dr Cleaver, had large subcutaneous hemorrhages and bleeding from the bowel. The condition could not be diagnosed, there was in addition an enlarged spleen and liver and the history of fever some months previously. The points of interest were that the platelet count was but 21,000, and the plasma did not clot at all on the addition of calcium, at least not sufficiently to allow the vial to be turned over. The whole blood also did not clot solidly. There was no excess of antithrombin, and the addition of calcium and of fibrinogen did not hasten coagulation in vitro. Fibrinolysis was present.

If we exclude cases showing markedly delayed coagulation time from the group of purpuras, this case cannot be considered purpura, if at the same time we consider a deficiency of platelets as incompatible with hemophilia, the case must rest unclassified. Although, as Howell states in the article referred to above, "the main distinguishing feature of the hemophilic condition is the greatly delayed coagulation time of the blood," it is seen that other diseases can bring about this disturbance of clotting to the same degree.

When we turn to a consideration of the rôle of the blood vessels in the hemorrhagic diseases, we begin to tread on still more uncertain ground. Very little is known of this factor in hemorrhage, and yet it is clear that it not only plays a part, but must play an important part. The capillary resistance test must depend on an abnormal permeability or weakness of the vessel wall, and its almost regular occurrence in purpura necessitates the deduction that the vessels are involved in this disorder. In the course of our study we have encountered, from time to time, cases in which hemorrhage occurred which seemed to be the result of vascular weakness. This lack of stability of the vessel wall



would seem to be a congenital defect, if we may judge from its manifestation in early life. The following cases can best be explained on the basis of a weakness or fragility of the vessel walls.

Bessie B., a child 3 years old, developed pertussis last year at the time of an epidemic which attacked about eighty children. She had a moderately severe case. Nevertheless she was the only child who developed subconjunctival hemorrhages. These effusions showed themselves from time to time in the course of the disease, following a paroxysm of coughing. The coagulation time of the plasma was normal, platelets also normal, 324,000, capillary resistance test positive, v. Pirquet positive.<sup>9</sup>

We attribute the hemorrhages in this case to the additional strain put on weak vessels at the time of the paroxysmal cough. In a measure this results in a spontaneous or automatic capillary resistance test. The case which we next cite is to be interpreted in the same way.

At the Willard Parker Hospital there are about twenty children who have to wear permanent intubation tubes on account of laryngeal obstruction. These children are frequently intubated. One of this unfortunate group always develops petechiae of the face and neck following the insertion of the tubes, which causes some struggling and marked venous congestion. The plasma of this child clots in the normal time, the platelets are not deficient. This is the only child who manifests this phenomenon.

As is well known, many of the infectious diseases lead to a rash, which is more or less hemorrhagic. Scarlet fever may be cited as a notable example of a disease in which the exanthema is petechial. A few petechiae are frequently present also in measles. We have had an opportunity of testing numerous cases of scarlet fever by the capillary resistance test and have found it in most cases positive, becoming negative again during convalescence. Although we do not care to agitate the interesting but highly hypothetical topic of vascular toxins, we may venture the opinion that these petechiae are due to a temporary lesion of the blood vessel wall. The fact that the petechial rash is not always in direct relation to the severity of the disease would suggest an individual susceptibility of the vessels. Here again the blood platelets were found normal and the coagulation of the plasma not delayed. (Table 5.)

The blood vessels may be abnormally weak and, as we have shown, yield to an undue pressure as in pertussis, they may be rendered permeable as the result of the infectious disease, or a similar result may be brought about by nutritional disturbances. This phase of the problem was studied recently in connection with infantile scurvy and

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<sup>9</sup> There seems to be some significance in the fact that of the seven children in the institution which we have been observing on account of a tendency to develop "black and blue" marks, four give a positive tuberculin reaction. Their blood coagulates in normal time. The ecchymoses appear especially in the spring, the season when tuberculous meningitis and phlyctenulae occur most often.

reported on elsewhere<sup>8</sup> This investigation led to the conclusion that the hemorrhagic manifestations of this disorder—the subperiosteal bleeding, the cutaneous petechiae, the red cells in the urine—cannot be accounted for by disturbances of the blood itself The blood coagulates in normal or almost normal time, there is no increase in antithrombin nor a decrease in the platelets On the other hand, the puncture test and the capillary resistance test are almost always positive This involvement of the vessel wall may not be elective, but merely part of the general tissue change in this disorder We have incorporated

TABLE 5—COAGULATION TESTS OF PLASMA

Type of Case	Drops of Calcium Chlorid (0.5 Per Cent)	Coag Time (5 Drops of Oxalated Plasma) minutes
Infantile scurvy	1	12
	2	10
	3	9
	4	9
	5	9
Child showing frequent "black and blue" marks	1	6
	2	6
	3	6
	4	6
	5	8
Hemorrhagic measles	1	7
	2	6
	3	6
	4	6
	5	6
Normal	1	7
	2	6
	3	6
	4	6
	5	7

in a table (Table 5) coagulation tests of a case of infantile scurvy, of hemorrhagic measles, and of plasma from a child with a tendency to nose bleed and ecchymoses It will be noted that the plasma coagulated in normal time, that of the scurvy case being slightly delayed

From time to time in the course of this paper, tests for antithrombin have been referred to It will be well, therefore, before concluding, to say a word about this substance and its estimation Some years ago, Weil, of Lyons, who was the first to venture to carry out venepuncture in hemophilia, suggested that the retarded coagulability in this disorder was due to an excess of antithrombin Since then it has

been demonstrated, however, that such is not the case. The tests in Table 6, which show the effect of the addition of normal and of hemophilic antithrombin to normal blood, are a convincing illustration of this fact. It will be noted in this table that a specimen of blood which clotted in five minutes, acquired a coagulation time of twenty-one minutes when one drop of antithrombin was added, irrespective of whether the antithrombin was from a normal person or from a case of hemophilia. This was likewise true in another specimen of normal blood (Dr B)<sup>10</sup> which was similarly tested. For tests of plasma antithrombin the method of Howell was employed, which consists of rendering inactive the prothrombin in plasma by means of a degree of heat which at the same time will not destroy the antithrombin. A fibrinogen solution is added to this heated and filtered plasma, and then the number

TABLE 6—EFFECT OF ADDING ANTITHROMBIN OF NORMAL AND HEMOPHILIC INDIVIDUALS TO NORMAL BLOOD

Substance Added to Blood	Normal Blood I (Dr B) Coagulation Time (10 Drops) minutes	Normal Blood II (Dr R) Coagulation Time (10 Drops) minutes
One drop Ca (0.5 per cent)	5	
Two drops fibrinogen	10	6½
One drop <i>normal</i> antithrombin	10	7
Two drops <i>normal</i> antithrombin	21	30
One drop <i>hemophilic</i> antithrombin	+	+
Two drops <i>hemophilic</i> antithrombin	21	30
	+	+

+ No clot

of drops of thrombin is determined which it is necessary to add to bring rapid coagulation. A test of this kind is shown in Table 7. We see a comparison of the blood of a child with a "bleeding tendency," of a normal individual, and of the atypical hemophilia (*calcipriva*) mentioned above. This test shows that the absolute amount of antithrombin in this case of hemophilia was at times in excess. It varied considerably from time to time, suggesting that there may be a peculiar interrelationship between calcium and antithrombin. In addition to the Howell test, we made use of an antithrombin test described by me,<sup>11</sup> which has the advantage of being simple, as normal plasma is employed instead of solutions of fibrinogen and of thrombin.

<sup>10</sup> This table also shows that the addition of a solution of calcium or of fibrinogen retards rather than hastens the coagulation of normal blood.

<sup>11</sup> Hess, A. F. Jour. Exper. Med., 1915, xxi, 338.

## CONCLUSIONS

The main points in the preceding article may be summarized as follows. The coagulation time of the plasma in hemophilia at times may become normal without the occurrence of hemorrhage or other apparent change in the condition of the patient.

The estimation of the number of blood platelets is of great value, as has been found by others, in differentiating between purpura and hemophilia. In some cases of purpura, the platelets are abnormal and may be differentiated, like other macrocytes and microcytes of the blood, into *macroplatelets* and *microplatelets*.

TABLE 7—ANTITHROMBIN TESTS OF PLASMA

Type of Case	Thrombin in Drops	Coagulation Time minutes
Hemorrhagic tendency	1	6
	2	4
	3	4
	4	2
Normal	1	18
	2	6
	3	4
	4	2
Hemophilia calcipriva	1	66
	2	16
	3	7
	4	5

The puncture test—the reaction following subcutaneous puncture of the skin—is an aid to diagnosis. In hemophilia a hemorrhagic area rarely results from this procedure, in purpura it is the rule.

The capillary resistance test is also of value. By this is understood the reaction following the application for a definite period of a tourniquet to the upper arm. In purpura, this results in petechial hemorrhages on the forearm, in hemophilia the effect is negative.

There is an *hereditary purpura* as well as hereditary hemophilia. This type of purpura should be more generally recognized, so that these cases will not, on account of their hereditary history, continue to be regarded as hemophilia.

*The male member of a family may be a bleeder of the hemophilic type and the female of the purpuric type.* Two families are described in which one member suffered from hemophilia and another from purpura.

Hemophilia may be atypical. A case is reported which showed a calcium deficiency, as borne out by various chemical and clinical tests (hemophilia calcipriva)

In some cases manifesting hemorrhage, the vessels seem to be involved. This weakness is encountered in children and may be congenital, it may appear in the course of an infectious disease, or of a nutritional disorder, such as infantile scurvy.

In the classical case the differentiation between hemophilia and purpura is simple. The picture of a typical hemophiliac is a male, with a hereditary history of bleeding, whose blood manifests a definite delay in coagulation time, whose platelets are normal in number, "bleeding-time" not increased, who shows no hemorrhagic reaction following subcutaneous puncture of the skin, and a negative capillary resistance test. A typical case of purpura is found to be quite different: the patient may be a male or a female, the plasma coagulates in almost normal time and the number of blood platelets is decreased (frequently below 100,000 in number), there is definite subcutaneous hemorrhage following puncture of the skin, an increase of the bleeding time, and the development of a large number of petechial hemorrhages following the application of a tourniquet.

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# EVENTRATION OF THE DIAPHRAGM

WITH REPORT OF A CASE OF RIGHT-SIDED EVENTRATION

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Among the lesions of the diaphragm, none has passed into the literature under more synonyms than the condition commonly called "*eventration*" Since 1849, when Cruveilhier introduced his conception of the disease under this term, the names "dilatation," "relaxation" (Wieting), "insufficiency" (Franck), "high position," "elevation" (Griffin), have been used to designate a pathological state of the diaphragm, characterized by a general expansion of one half of the organ, allowing the abdominal viscera to be displaced upward into the thoracic cavity The diaphragm is greatly thinned as well as distended, but its three layers remain intact, and there is no solution of its continuity In this essential respect, the condition is different from hernia of the diaphragm, which, whether true or false, depending on the presence or absence of a hernial sac, consists of a localized opening in the sheet of the diaphragm, through which the abdominal viscera pass into the thoracic cavity All of the terms mentioned are partially descriptive, though none is satisfactory While the commonest of them, "*eventration*," is a gross misnomer, since it suggests the displacement of the viscera out of the abdomen, it has received by custom a connotation which is specific for this condition of the diaphragm The other terms are so ambiguous that if any one of them were accepted, it would yet have to acquire a long usage to gain the special meaning needed in this connection As its multiplicity of names suggests, eventration is one of the rare lesions of the diaphragm The latest statistics of its frequency as compared with other types of hernia of the diaphragm, published by Eppinger in 1911, show the following incidence

TABLE 1—FREQUENCY OF HERNIA AND EVENTRATION

Type of Diaphragmatic Hernia	Right Side	Left Side
Hernia vera	21	53
Hernia spuria	34	527
Eventratio	2	15

Total cases of hernia, 635    Total cases of eventration, 17    Ratio of eventration to hernia, 1 to 37

\* Submitted for publication Oct 11, 1915

\* From the Medical Clinic of The Johns Hopkins Hospital

Since the compilation of these figures, many cases of hernia have been reported, and the number of cases of eventration has risen to forty-five. But the relative incidence of these lesions has probably remained so constant that this proportion is still a fair index of the rarity of the condition. This table is further interesting in showing the relative infrequency of hernia and eventration of the right side of the diaphragm. The case to be reported in this paper is thus seen to be the third example of right-sided eventration.

Thirty-one cases of eventration of the diaphragm were collected and summarized by Bergmann in 1913. A review of the literature, however, reveals several reports omitted by him and, in addition, several published since his article. The following is a tabulation of forty-five case-reports—forty-four gathered from the literature and one new case, reported in this paper.

#### REPORT OF CASE

*Diagnosis*—*Eventration of the right side of the diaphragm. Congenital malformation of the mesentery, with mesenteric hernia. Chronic intestinal obstruction.*

*History*—J. B., a white male, aged 52, was admitted to the Medical Clinic of The Johns Hopkins Hospital, November 16, 1914. General No. 99055. Complaint, "Pain in the upper right side of the stomach."

The patient came from healthy stock and was the father of five normal children. In general his health had been robust, except for typhoid fever, complicated by pneumonia, when he was 19 years old, he had not been incapacitated by any acute infectious disease. In his occupation as a sailor, chiefly around harbors, he had led an active life. He was not addicted to the use of alcohol or tobacco.

Throughout his life a "sensitiveness of the stomach" had necessitated a moderate degree of care in the selection of his diet. In 1909, five years ago, he began to have "indigestion," associated with constipation and pains in the upper right quadrant of the abdomen. This pain was "knife-like," extending from the midline to the axilla, above the umbilicus and below the costal margin. The pain could be relieved by pressure on that side of the abdomen. The pain recurred at irregular intervals, and sometimes was accompanied by nausea and vomiting. He was never jaundiced and did not have tarry stools. He had not been dyspneic. Lately the pain has recurred more frequently and has radiated into the right shoulder. This has incapacitated the patient, and he has lost 17 pounds in the past five months.

*Physical Examination*—The patient, a large-framed, well nourished man, is neither dyspneic, cyanotic, nor jaundiced. The general examination is unimportant, except as regards the thorax and abdomen.

*Thorax*—The thorax is deep, with a wide costal angle. Both sides expand equally, by measurement, the right from 45 to 47 cm., the left from 45 to 46 cm. On the left side there are no abnormal signs. On the *right side*, vocal fremitus is not palpable in the axilla. The percussion note at three successive levels changes from resonance to flatness and to tympany. The note is resonant over the upper right front and back. At the third rib it becomes dull, and below this it is flat to the level of the fifth rib. From the fifth rib downward the note has a dull tympanitic quality, until the full abdominal tympany is reached. At the base posteriorly the lower border of pulmonary resonance is 10 cm. higher on the right than on the left, and only slight descent of this is percepti-

ble on the right. A tympanitic area occupies the usually dull region of the lower ribs in the back. Litten's sign is absent in the right axilla. On auscultation, enfeebled breath sounds are heard over the upper portions of the right lung. These sounds gradually diminish until below the level of the fourth rib the sounds of breathing and of voice are inaudible. There is no egophony.

**Abdomen.** The abdomen is not distended, but on the right side the muscles are resistant. Varying irregular masses are palpable in the right upper quadrant, in a region which is painful when pressed on. The edge of the liver cannot be felt, and the area of hepatic dulness seems to end at the level of the fifth rib. In the region of the lower ribs behind, the percussion note is tympanitic, as it is over the front of the right upper quadrant. On the left side there is a small inguinal hernia. *Inflation of the colon*, by pumping air into the rectum, causes the abdomen to become distended, while the level of tympany on the right side is advanced upward an interspace. This distention causes pain like the distress which characterizes the patient's illness.

*Results of Special Examinations*—Gastric Analysis. Free HCl, 34, total acidity, 72.

Feces normal. Urine normal.

Wassermann reaction negative. R. B. C., 4,792,000, Hb., 72 per cent, W. B. C., 7,440. Widal test negative. Conjunctival tuberculin test, 5 per cent, slightly positive.

**Heart.** The heart is not enlarged or displaced. The electrocardiogram (Film H-09) shows "normal rhythm, with no abnormal complexes. Conduction time 0.18 second. There is a progressive decrease in the size of the R-wave. Normal electrocardiogram."

As the result of these examinations, Dr. Janeway excluded thickened pleura, which among other conditions had been considered the likely explanation of the abnormal physical signs over the right side of the chest, and made the diagnosis of eventration of the right side of the diaphragm. This conception was strengthened by the following radiographic studies, and when confirmed at subsequent operation, proved to be the first instance of the *intra vitam* diagnosis of this condition.

**Roentgenologic Findings (Dr. Baetjer and Dr. Waters)**

**Thorax (Plate 26278 Fig 1)** The lung shadows are normal. The dome of the right diaphragm is very high, reaching approximately the level of the third rib in front. It is normal in shape.

The *fluoroscopic* examination shows on the right side a high diaphragm, which is normal in shape. On deep respiration the movement of this side is paradoxical, it moves upward during inspiration and downward during expiration. The left side of the diaphragm moves freely in long sweeps downward during inspiration. The heart appears to be normally placed. The stomach is in a high position with its pylorus under the right costal margin. The colon, filled with bismuth, shows double and complicated kinking on the right side.

**Large Intestine (Plate 26196 Fig 2)** This shows the descending colon and the splenic flexure in their normal situations. The transverse colon is prolapsed, and in the right upper quadrant it is looped and doubled on itself. On the right side of the plate there is no shadow to indicate the position of the ascending colon.

These evidences of abdominal disease confirmed the impression that a chronic inflammatory condition, possibly cholecystitis, was present in the right upper quadrant. Because of this, an exploratory laparotomy was performed by Dr. J. M. T. Finney, Dec 4, 1914. The following is the summary of the note of operation (see Fig 3).

Neither the liver nor the gallbladder is visible through the right rectus incision. The gallbladder is found roughly a hand's breadth above the costal margin, at the level of the sixth rib. It is normal. The liver, slanting downward and to the left, looks normal, but is situated high up under the ribs.



Case No	Year	Author	Sex*	Age	Side Affected	Chief Clinical Findings
1	1784	Pyl	♂	1 da	Left	Death soon after birth Cyanosis
2	1790	Petit	♂	ad	Left	"Asthma, after eating"
3	1819	Meckel	♂	1et	Left	
4	1829	Laennec	♂	ad	Left	
5	1837	Froriep	♀	19	Left	Dyspnea and digestive disorders for 14 years
6	1852	Lawrence	♂	33	Left	Practically no symptoms
7	1867	Marsh	♂	33	Left	No history
8	1882	Thoma	♂	75	Left	No history
9	1894	Tennant	♂	60	Left	No history
10	1900	Crispino	♀	55	Left	Gastro intestinal disorders Fractured arm
11	1901	Struppler	♂	26	Left	Life long cough Dyspnea after trauma P eal signs of hernia Roentgen ray sign
12	1901	Neisser	♂	42	Left	eventration Bronchiectasis Signs of intestines in
13	1902	Doering	♂	60	Left	chest Roentgen ray of eventration Dyspnea many years Signs of hernia
14	1902	Fraenkel	♂	49	Left	Dyspnea and hemoptysis several years S
15	1903	Glaser	♂	39	Left	of hernia by phys exam and Roentgen
15	1905	Hildebrand and Hess	♂	20	Left	Incarceration symptoms for many y Famous case of "Sch "
16	1905	Saller and Rhein	♂	20	Left	Signs of subdiaphragmatic gas abscess
17	1906	Wieting	♂	50	Right	Symptoms of gallstones Operation
18	1907	Kienbock	♂	54	Left	Trauma to right side years previously S
19	1907	Herz	♂	36	Left	of hernia Roentgen ray of eventration Cough, Typical signs of eventration
20	1908	Arnsperger	♀	20	Left	No symptoms All signs of eventration
21	1909	Koniger	♀	27	Left	Dyspnea and pain several years The u signs of eventration
22	1910	Otten and Scheff old	♂	68	Left	Paradoxical dysphagia Usual signs
23	1910	Beltz	♂	70	Left	Dyspnea, pain in left side, gastric disord
24	1910	Beltz	♀	34	Left	Typical findings No history
25	1911	Scholz	♂	1	Left	Slight dyspnea and indigestion
26	1911	Eppinger	♂	35	Right	Typical signs of eventration Case not s in life
27	1911	Franek	♂	73	Left	Right hemiplegia 12 years Ohronic const
28	1911	Appel	♂	60	Left	tion Typical eventration Dyspnea 2 years Typical eventration
29	1911	Becker	♂	25	Left	Life long gastric discomfort Typical
30	1912	Scheidemandel	♂	21	Left	Pain between shoulders Usual signs
31	1912	Scheidemandel	♂	55	Left	Cough 36 years Typical signs
32	1912	Malkow	♂	45	Left	Typical signs, according to Bergmann
33	1913	Bergmann	♂	60	Left	Gradual onset of dyspnea Typical
34	1913	Kryser	♀	28	Left	No symptoms Typical findings
35	1913	Haase	child	3 mos	Left	Cough and dyspnea Typical findings
36	1913	Reuss	♂	46	Left	Injured left side Typical findings
37	1913	Baetge	♂	64	Left	Dyspnea and palpitation many years Typi signs of eventration
38	1913	Baetge	♂	28	Left	Gastro intestinal disorders Typical eventrat
39	1913	Baetge	♂	41	Left	Dyspnea and stomach trouble since childho Typical signs
40	1913	Motzfeldt	♀	41	Left	Practically same as Case 39
41	1913	Krause	♂	42	Left	Gastric disorders Typical signs
42	1913	Krause	♀	36	Left	After pregnancy Typical signs
43	1914	Manges and Wessler	♂	35	Left	Gastric crises, dyspnea, cyanosis Typical sig of eventration
44	1914	Fischer	♂	30	Left	Found at conclusion of typhoid fever comp cated by pneumonia
45	1915	Author's case	♂	52	Right	Painful febrile periods suggesting gallbladd disease Tympany over lower right ches Right diaphragm by Roentgen ray at third r

Associated anomalies	Probable Etiology	Cause of Death	Condition of Diaphragm—Neeropsy	Remarks
	Congenital		Whole side a thin membranous sac	
	Acquired?	Peritonitis	Whole side thin and distended	Cruveilhier's case
	Congenital		One half diaphragm a thin sac	
			Same as above	
	Congenital		Thin distention of whole side, with three layers intact	
	Congenital	Pneumonia	Thin aponeurotic expansion of entire left half of diaphragm	
	Congenital	Pneumonia	Same as above	
Unilateral femoral and pelvic herniae	Congenital	Peritonitis	Pleura, peritoneum and a little fibrous tissue representing the diaphragm	
	Congenital	Pneumonia	Thin, distended sac	
Electrocardia	Congenital	?	Left diaphragm some inches higher than the right	
	Acquired?			Shown by Arnsparger to be eventration
	Congenital			Atrophy of lung
lobed left lung	Congenital		Thin membranous sac of whole side with usual layers	Lung not compressed
	Congenital	Cancer of tongue	Thin sac, showing "lipomatous pseudohypertrophy"	Benda's case
Small left lobe of lung	Congenital	Peritonitis	Thin sac formed by whole of left side of diaphragm (Eggeling)	Intragastrie pressure
Small left lung	Congenital	Typhoid fever	Thin sac, with few muscle fibers	
	Congenital	P y o n e phrosis	Thin sac with liver and stomach, ruptured by perforated gastric ulcer	First case of right sided eventration
	Acquired			
	Congenital			
	Congenital			
	Congenital			
	Acquired			Example of chronic "magenblase"
	Acquired?	Pneumonia	Saccular distention of whole side	Atrophy of phrenic nerve
	Congenital			
	Congenital		Diffuse expansion of right side	
	Congenital			Paradoxical movement
	Congenital			
	Congenital			
	Congenital			
	Congenital			Diphtheria at 20
	Congenital			
	Congenital			Syphilis
	Congenital			Purpura
	Congenital			Pneumonia
	Acquired?			Jamin's sign
	Congenital			
	Congenital		Relaxed, elevated diaphragm found at operation for gallstone	Electrocardiogram Cardiorenal
	Congenital			
Unilateral left lung Dextrocardia	Congenital	Nephritis	Atrophy and fatty change of distended left half of diaphragm	Anomaly of mesenteric arteries
	Congenital	?	Sac like left diaphragm	Phrenic atrophied
	Acquired			
	Acquired?			
	Acquired?		Thin, dilated diaphragm, found at operation	
Malformation of mesentery	Congenital	Pulmonary embolism	Thin distention of whole right side of diaphragm reaching level of R 3, found at operation	Paradoxical movement

The hand passed over the dome of the liver touches the third rib in front, and by slight pressure the second interspace can be reached. The diaphragm is thin, but otherwise normal. It can be felt to cover the liver smoothly, and has no localized bulging or solution of continuity.

The stomach is normal, but has its pyloric end high under the right costal margin. The transverse colon is redundant and together with a loop of small intestine passes through a hernia in the root of the mesentery. In this anomalous formation of the mesentery there are large dilated veins and an aberrant artery. The cecum is high under the costal margin on the right side.

From these notes and from a sketch made at the operation, Mr. Brodel elaborated the drawing reproduced as Figure 3. This shows clearly the anatomical relationships of the high diaphragm and the displaced viscera, and at a glance, offers the explanation of both the gastro-intestinal symptoms and also the physical signs over the chest and abdomen.

The patient progressed well for ten days after the operation, when suddenly he became dyspneic, spat blood, and died after a few minutes, with symptoms of pulmonary embolism. As a necropsy was not permitted, no further examination of the diaphragm was possible.

#### DIFFERENTIAL DIAGNOSIS

Previous discussions of the differential diagnosis between eventration and conditions presenting similar signs have been limited to the consideration of left-sided lesions. The case just described directs emphasis on the diseases of the right thoracico-abdominal section of the body. At the same time, however, completeness and clarity require a review of the findings in the left-sided cases.

In the case described herein, the abdominal symptoms were the urgent cause of the patient's coming to the hospital. The intermittent periods of pain in the right upper quadrant, associated with vomiting and fever, made it seem likely that there was some chronic inflammatory disease in that region. Among the diagnoses considered were duodenal ulcer, with perforation and a localized gas abscess beneath the right lobe of the liver, kinking of the transverse colon, producing intestinal obstruction, and cholecystitis. This last diagnosis was considered the most probable, and was the point determining the operation on the patient. The mesenteric hernia, found at operation, must have produced frequent mild incarcerations of the intestines passing through it. This explanation is sufficient to permit the dismissal here of this phase of the subject.

In the absence of signs of fluid, thickened pleura over the lower part of the right chest was thought at first to be the cause of the dulness on percussion, the diminution of the breath- and voice-sounds, the absence of fremitus and of Litten's sign in the right axilla. However, the exact location of the flatness and of the complete loss of vocal sounds over a region from the third to the fifth ribs, lying between normal lung resonance above and a curious area of tympany below, made it seem more likely that this region was occupied by the liver. Inflation of the colon displaced this area of dulness upward.

and increased the tympanitic region below, as would occur with a semimovable organ like the liver lying in the relaxed and elevated dome of the diaphragm, but which would not occur in thickened pleura. The most closely allied condition, which would give some of these signs, is hernia of the right side of the diaphragm. Of this lesion, for comparison, we have only one case—perhaps the only case diagnosed during the life of the patient—namely, that reported by Dietlen and Kneirim. In their case, the stomach and some coils of intestine passing through the diaphragm into the thoracic cavity, lay above the liver. Here, the area of tympany across the chest, lay between normal lung resonance and the area of hepatic dulness. Changes in the position of the patient and the ingestion of fluids and gases somewhat modified the sounds elicited by percussion and auscultation over the tympanitic area, giving almost the reverse order of the two lower strata of physical signs noted in our case of eventration of the diaphragm.

In our case, the radiographic and fluoroscopic examinations confirmed the clinical impression of eventration of the diaphragm. The left side appeared to be normal, while the right showed a smooth shadow arching upward across the thorax to the level of the third rib (Fig 1). Above this shadow, normal pulmonary shadows were visible, while below it, the stomach and intestines, when filled with bismuth, could be clearly seen. This contrasts sharply with the roentgenograms in hernia of the right side of the diaphragm. In Dietlen's and Kneirim's case, a bright area was seen between the lung shadows and the black hepatic region. When bismuth paste was administered, the peristaltic shadows of the stomach and small intestine obliterated this bright idea (Fig 4). The movement of the diaphragm in these two cases is so contradictory that it indicates the doubtful value of this sign in the differentiation of eventration from hernia of either the right or the left side of the diaphragm. In 1898, Kienbock observed paradoxical movement of the diaphragm by the fluoroscopic screen. This form of motion is characterized by inspiratory elevation and expiratory descent of the affected side of the diaphragm. Though it is found in numerous conditions, such as pleurisy with effusion, and pyopneumothorax, it was observed in a case of hernia of the left side of the diaphragm, and seized on as one of the definite radiosopic signs of this condition. In our case of eventration, the movement of the thin distended side of the diaphragm was paradoxical in character, while in the case of hernia, the movement of the upper borders of the diaphragmatic shadows was normal, descending with inspiration and rising with expiration. Before this, however, Lotze's case had proved that the differential diagnosis between hernia and eventration cannot

be made with absolute certainty by means of the Roentgen ray. He described what seemed to be a typical example of eventration of the left side of the diaphragm, in which the respiratory excursions of the diaphragm were normal, though diminished. Several years later, when Risel performed the autopsy on this patient, he found an old hernia of the left side of the diaphragm, with the rest of the organ practically normal.

A most decisive differential fact may be gained from the study of the intragastric pressure, according to the method of Marey and



Fig 1 (Roentgen-Ray Plate 26278) —Thorax showing the dome of the left diaphragm, normal in outline, arching to the level of the third rib in front. Above this are normal lung shadows, and below the hepatic shadow is a bright area occupied by the intestines displaced upward. On the left the heart and diaphragm are in normal position.

Schlippe. By the application of this method, Hildebrand and Hess correctly diagnosed as eventration of the left side of the diaphragm, the famous case of "Sch," which, for a period of twelve years, was studied in many clinics as an example of hernia. By suitable instruments, a record is made of the respiratory phases of the pressure within the stomach, to determine whether the organ is situated within the abdominal or thoracic cavity. If the stomach is in its usual place,

the pressure within it rises during inspiration and falls during expiration, synchronously with the intra-abdominal pressure. If, however, the stomach lies in the thoracic cavity, the curves are reversed, the pressure falls during inspiration and rises during expiration, synchronously with the changes in the intrathoracic pressure. This investigation was not made in our case, but Diellen and Kneiss found that

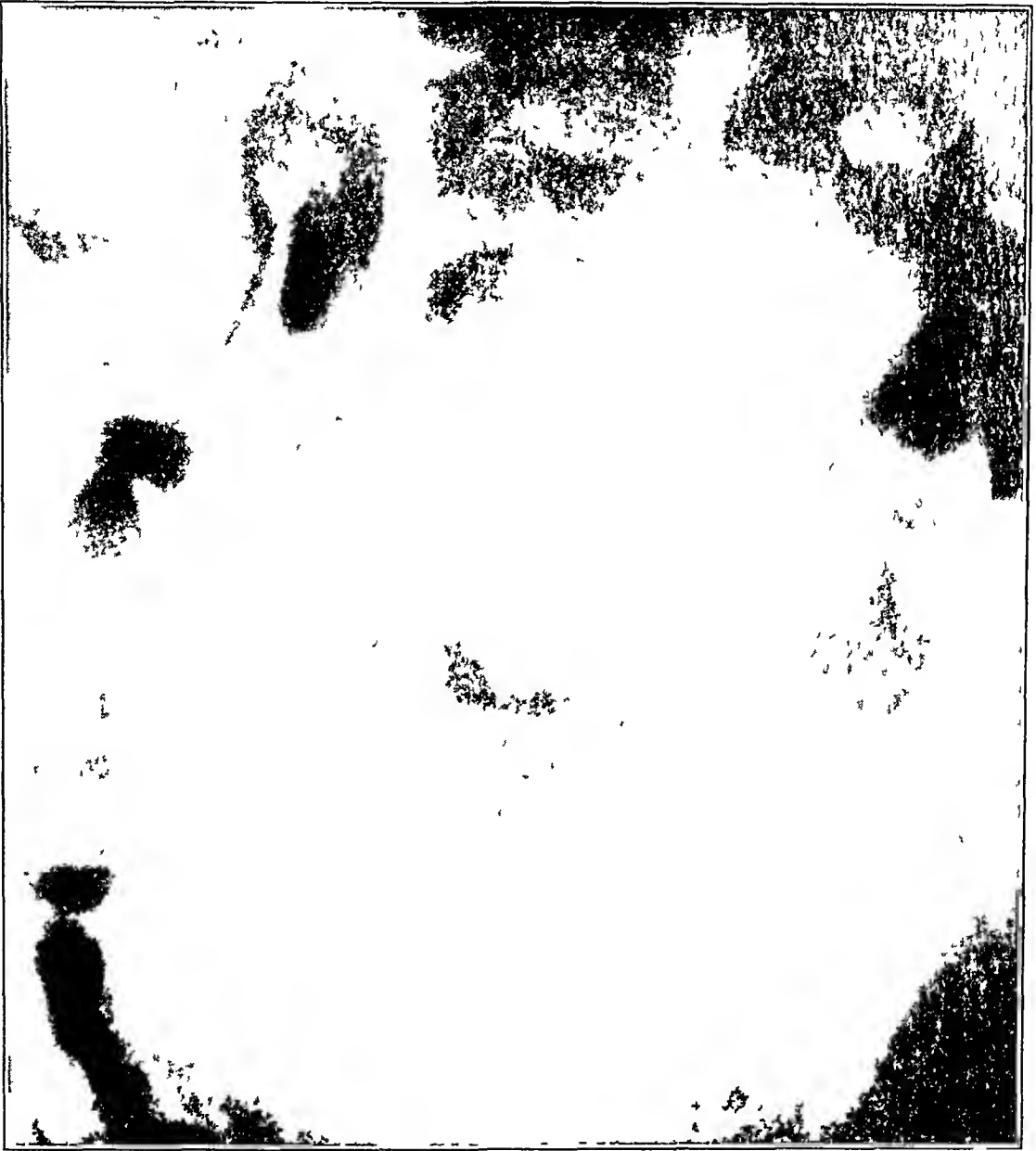


Fig 2 (Roentgen-Ray Plate 26196) —Bismuth in the large intestine. This shows the prolapse and kinking of the transverse colon in the upper right quadrant, with absence of shadow of the ascending colon on the right side.

the intragastric pressure varied according to the intrathoracic formula in their case of hernia.

When, in Table 2, it is stated that a case exhibited typical physical the following are implied. A normally formed thorax, with somewhat and radiographic signs of eventration of the *left* side of the diaphragm,

diminished expansion on the left side, normal physical signs on the right side, except for the usual evidence of displacement of the heart to that side, normal pulmonary resonance and vesicular breath-sounds over the upper half of the left side, but below the level of the fourth rib, in front and behind, a tympanitic note, absence of voice and breath-sounds, absence of vocal fremitus, and absence of Litten's sign in the left axilla, in place of respiratory murmur, splashing and metallic sounds elicitable over the lower left chest, with great variation in these according to the degree of fulness of the stomach. These physical signs may be given wholly or in part by (1) hydropneumothorax or pyopneumothorax, (2) subphrenic gas abscess, (3) large cavity in the lower lobe of the left lung, (4) paralysis of the diaphragm, and (5) hernia of the diaphragm. The differentiation by simple physical examination between these conditions is almost impossible. Many of the cases of eventration have been explored with the aspirating needle under the supposition of pyopneumothorax (Sailer and Rhein). While the signs here may be similar, the history and general condition of the patient with eventration are different from those features of the other diseases. In eventration, there is not likely to be the sudden onset, great dyspnea and fever that characterizes pyopneumothorax. In subphrenic gas abscess, such as occurs with a walled-off perforation of an ulcer of the stomach, Litten's sign may be still visible in the axilla, while the general condition indicates an acute septic state rarely present in eventration. But in these states, as in hernia, the greatest assistance in diagnosis is derived from investigation by the Roentgen ray.

These differential radiologic findings have been summed up by Becker in a beautifully illustrated paper, as follows:

In both hernia and eventration a delicate bow-shaped line may be seen arching upward across the left side of the chest. In *hernia*, the contour of this line is irregular, partly distinct, partly blurred, it usually shows a paradoxical respiratory movement, when the stomach and intestines are filled with bismuth, extreme derangement of the line is caused by the new shadows, and when the stomach is inflated with CO<sub>2</sub> the line shows practically unlimited extension upward, along with obvious displacement of the stomach, and the lung shadows can be seen through the bright area of the inflated stomach. In *eventration*, the contour of the line is that of a smooth, sharply defined bow-shaped shadow, with a bright area below and lung-shadows above, the movement is usually normal but diminished, when the stomach and intestines are filled with bismuth, the new shadows take a restricted dome-like position, and when the stomach is inflated there is only a smooth distention, limited by the bow-shaped line, while the lung shadows remain entirely above this line and are not visible through the "stomach-bubble."

While all of these facts together may make the diagnosis almost positive, none is pathognomonic. The diagnosis rests on the phenomena exhibited by the patient as a whole.

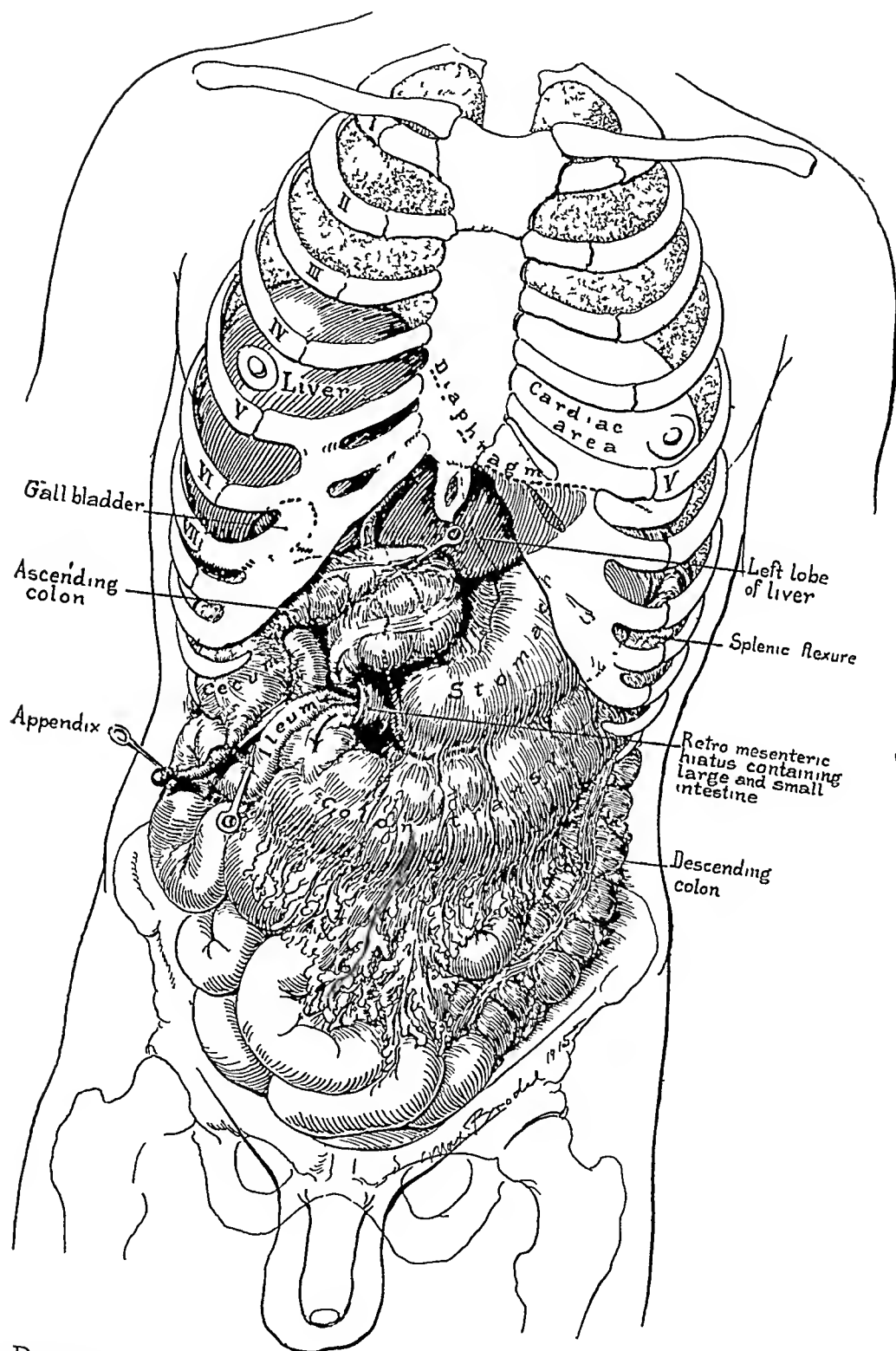


Fig 3—Diagram by Max Brodel from sketch at operation This shows the high-position and eventration of the right side of the diaphragm, the mesenteric anomaly and its hernia, and the malposition of the cecum and ascending colon



The tendency is to exclude paralysis of the diaphragm, with consequent loss of tone and high position, from the category of eventration. These cases are usually fatal or improve before the typical clinical and anatomical picture of eventration is produced. Important in this connection is the study of the electrical condition of the phrenic nerves by Jamin's method of faradization of the phrenics in the neck. During the stimulation of the nerve, movements of the diaphragm may be observed by fluoroscopy. By this means, the presence or absence of degeneration of the nerve can be determined, and also an estimate of the muscular condition of the diaphragm can be made. These, however, are the limits of the conclusions to be drawn from such observations, and the method cannot be used to differentiate definitely between hernia and eventration.

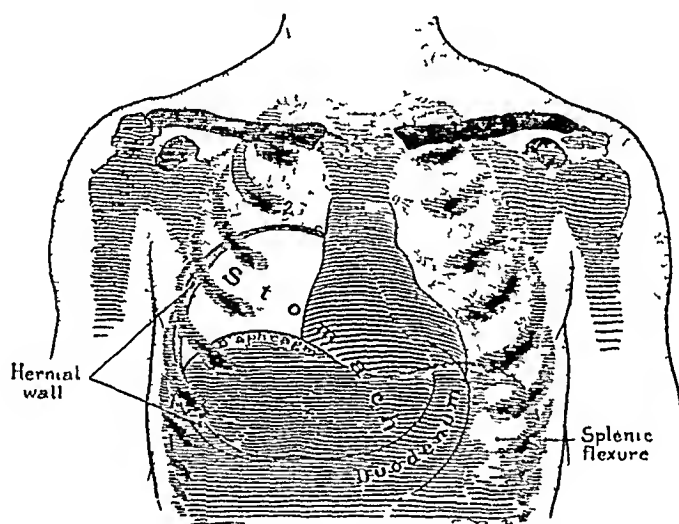


Fig 4—Schematic copy of roentgenogram published by Dietlen and Knierim to illustrate Roentgen-ray findings in hernia of the right side of the diaphragm. Here the clear stomach region lies between shadows of the lung above and the liver below. In eventration of the right diaphragm the liver shadow lies between the lung shadow and a bright area due to distended colon in the lower left chest.

#### PATHOLOGICAL ANATOMY

The pathological anatomy of the diaphragm has been studied at necropsy or operation in twenty-two cases of eventration. In all instances, whether the affection has occurred on the right or the left side, the diaphragm has been found to be a thin, translucent membrane. The peritoneal and pleural reflections have covered the sides of the diseased organs smoothly and uniformly. Between these membranes there has always been found a layer of fibrous tissue, which in some cases contained a few strands of muscle tissue and in others consisted of only a "thin aponeurotic sheet." In the case reported by Doering there was a fringe of normal muscle around the parietal attachments of the diaphragm, disappearing as the dome was reached. In Benda's

case the affected half of the diaphragm was distinguished by its opaque whitish color from the red, muscular aspect of the healthy side. Benda found that the strands of muscle fibers were replaced by parallel bands of fat cells, and he termed the process "lipomatous pseudohypertrophy," correlating it with one of the forms of myogenic muscular atrophy. The pathological anatomy of structures closely related to the diaphragm is variable. The phrenic nerves have been examined in a number of cases of eventration. As in Benda's study, they have been found to be reduced in size in comparison with the nerve of the healthy side, but have been composed of normal fibers, with no great evidence of degeneration in the nerve trunk or its nuclei. The pleura, peritoneum and blood supply of the diaphragm have not shown any abnormalities, and the attachments of the diaphragm have been normal. The lungs and abdominal viscera, however, have exhibited various developmental anomalies, which will be considered when the etiology of the condition is discussed. A significant fact, revealed at autopsy, is that while the diaphragm may be ballooned upward by the abdominal organs, the lungs are not compressed. The heart and mediastinum may be displaced to the right, or left. In fact, displacement of the heart to the right, simulating dextrocardia, is the invariable accompaniment of eventration of the left side of the diaphragm.

#### ETIOLOGY

When Cruveilhier established the category of eventration of the diaphragm, he regarded the condition as an acquired lesion. Thoma, on the other hand, published the hypothesis that the condition is a congenital anomaly of development. Since then, evidence in favor of each opinion has been adduced, but the majority of the authors, as shown in Table 2, have supported the hypothesis of the congenital origin.

In favor of the acquired nature of the disease, cases have been cited in which the condition has been apparently secondary to (1) pressure differences on the two sides of the diaphragm, (2) disease of the muscle, and (3) disease of the nerves. All of these may follow trauma, but each class embraces several specific diseases. It has been demonstrated that elevation of the dome of the diaphragm follows increased abdominal pressure. The chief states producing this are pregnancy, ascites, and chronic gastro-intestinal distention, such as meteorism and Hirschsprung's disease. If this factor of increased pressure in the abdomen bore an important etiological relationship to eventration, the frequency of pregnancy in general—and sometimes in the individual—should find a counterpart in a large number of women suffering from eventration of the diaphragm. Table 2, how-

ever, shows a surprising minimum of females among those presenting this affection. Among the other dynamic intra-abdominal causes of eventration, great importance has been attached by Hoffmann to chronic gaseous distention of the intestines in his hypothesis that "*chronische Magenblase*" produces at least "rudimentary eventration." His conception is that pressure on the diaphragm produces circulatory disturbances which lead to "loss of elasticity," degeneration of the muscle, and stretching of the organ. While it is conceded that "high position" may be produced in this way, it is doubtful whether the condition found in eventration actually results from this process. A strongly unfavorable criticism of this hypothesis is that bulging of the abdominal wall and ptosis of the viscera are the most common sequels of increased abdominal pressure, while in eventration, the tonus of the abdominal wall is at least normal. From the pulmonary side, retracting pleural adhesions may drag the dome of the diaphragm upward. Thoma describes a case in which this occurred, but he uses it as a contrast to true eventration, from which category he eliminates it along with similar cases of mechanical "*hochstand*" of the diaphragm.

The question of the etiological significance of disease of the muscle and nerves in eventration of the diaphragm is more difficult to settle. It is well known that in progressive muscular atrophy, the diaphragm becomes so degenerated and weakened that its loss of function may be the cause of death. But here, while the state of the diaphragm may resemble that seen in some cases of eventration, its evident part in a general disease differentiates it from the localized diaphragmatic lesion of eventration. In Benda's case, for example, although there was a "lipomatous pseudohypertrophy" of the atrophied muscle, there was no accompanying nerve lesion. Peripheral neuritis of the phrenic nerve, after diphtheria and other infectious diseases, and in toxic states like alcoholism and beriberi, has produced relaxation of the diaphragm and consequent high position. In practically all of these cases, however, the normal tone and position of the diaphragm has been regained when the nerve lesion improved (Behrenroth), or if death has occurred, the diaphragm has not shown the flaccid fibrosis characteristic of eventration.

The criteria of the congenital origin of eventration, as noted by Thoma in 1882, have gained validity from the studies of subsequent investigators. These points are chiefly (1) the coincidence of the frequency of eventration of the left side of the diaphragm with the complexity of the development of that side of the organ, (2) the occurrence of eventration in the fetus and the new-born, (3) its association with other congenital anomalies of the body, and (4) the usual absence of symptoms over long periods of time. Detailed

recapitulation of the embryology of the diaphragm would be more confusing than useful here, where all that need be emphasized is that the left side of the organ develops from a number of sources and is not entirely formed until some time after the completion of the relatively simple development of the right side. On the right, the liver, growing in the septum transversum, which early separates the pleural and peritoneal cavities on that side, seems to guard the right side of the diaphragm from developmental disturbances. The left side, however, grows in close association with the left lobe of the liver, the stomach and spleen, the pericardial formation, one of the pulmonary ridges, and the pleuroperitoneal membrane. In addition, the posterior portion of the left side of the diaphragm is the last to close. This undoubtedly accounts for the great predominance of congenital hernia of the left side of the diaphragm. By analogy, the great relative frequency of eventration of the left side suggests not only that this condition is associated with the developmental intricacy of that side, but also that it is a congenital abnormality. The finding of eventration in either fetuses or young children in four of the forty-five cases of the disease is good evidence in favor of its congenital origin (see Cases 1, 3, 25, 35 in Table 2). In nine cases (Cases 8, 10, 12, 13, 15, 16, 40, 45, Table 2), other abnormalities of the lungs or abdominal viscera were present. These were abnormally lobulated lungs, "stunted lungs," congenital hernias, and true dextrocardia. In the case described in this paper, the deformity of the mesentery and the position of the cecum under the right costal margin were clearly congenital abnormalities. This coincidence of rare anomalies suggests a common etiological relationship, namely, that eventration also is a congenital dystrophy. In connection with recent studies of body growth, Byloff has published papers on the thesis of high position of the diaphragm as a stigma of degeneration. He found moderate high position in a number of individuals who showed defective development of various organs and parts of the body. None of Byloff's examples is a case of eventration, but his work is capable of interpretation in favor of the congenital origin of this affection.

It has been noted, in the discussion of the pathological anatomy of eventration, that the lung lying above the distended diaphragm has not been compressed, although its thoracic chamber has been always greatly reduced. This uniform absence of compression of the contiguous lung is to be emphasized here as one of the strongest arguments in favor of the congenital origin of eventration of the diaphragm.

#### PROGNOSIS

It is probable that if the degree of eventration be extreme in the new-born, this condition is incompatible with life. After the first year, however, the disease is rarely a cause of death. While the

greatest number of cases have been found in individuals between the ages of 20 and 50 years, instances have been observed in patients in the eighth decade of life. Cardiorespiratory diseases have not been unusually frequent in those suffering with eventration of the diaphragm, but gastro-intestinal symptoms have been the most distressing feature. The danger of incarceration of the displaced abdominal viscera is the only element which renders the prognosis grave.

## SUMMARY

This paper reports a case of eventration of the right side of the diaphragm. This diagnosis, made from physical examination, is the first of its kind determined during the life of the patient. The clinical impression was confirmed at an operation.

Tabulation is made of forty-five cases of eventration of the diaphragm. Of these, three were right-sided, while forty-two were left-sided lesions.

In the differential diagnosis between eventration and allied states, the difficulties are pointed out, particularly with regard to the differentiation from hernia of the diaphragm. No single method is capable of establishing this differentiation, but all together render the diagnosis reasonably certain.

The various etiological hypotheses are summarized, showing that the weight of evidence is in favor of the opinion that the disease has a congenital origin.

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# A STUDY OF THE LIPIN CONTENT OF A CASE OF GAUCHER'S DISEASE IN AN INFANT

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Lipoid bodies play an important part in many pathologic processes, especially in those involving the spleen and lymph nodes and other blood-forming organs which, until recently, were not suspected of bearing any relation to the distribution of the lipins of the body. Cells which contain considerable lipid substances are usually characterized, in routine histologic sections, by the relatively large amount of pale, more or less uniformly vacuolated or honeycombed cytoplasm, and small rather deeply stained and often eccentrically placed nuclei. The vacuoles in the cytoplasm represent spaces left by lipid material that has been dissolved during embedding. In fresh tissue this material does not react typically to the various microchemical reactions for neutral fat. Clusters of such lipid cells have been frequently noted in chronic inflammations such as chronic aortitis and chronic salpingitis, especially where there is considerable lymphoid infiltration (Pick,<sup>1</sup> Krompecher<sup>2</sup>), but it is only in the recent work of Poscharisky<sup>3</sup> and Kusunoki<sup>4</sup> that fats and lipoids are described in considerable amounts in the spleen in association with various pathologic processes and, indeed, even in some normal conditions. This accumulation of lipoids in the spleen and other blood-forming organs promises to contribute considerably to the elucidation of Gaucher's disease and allied xanthelasmic processes in which the parenchyma of the hematopoietic organs is more or less replaced by distinctive large pale cells whose cytoplasm tends to be vacuolated.

Gaucher<sup>5</sup> described the first case of the disease named after him in 1882, and noted particularly the large pale cells which he considered

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1 Pick, Ludwig. *Über besondere Structuren in alten Eitertuben*, Berl klin Wchnschr, 1908, No 37

2 Krompecher. *Vergleich biologisch-morphologische Studien betreffend die Fibroblasten und Makrophagen (Eiterphagocyten, Pseudoxanthom-, Typ Gaucher-, Malakoplakie-, Rhinoskleronzellen) des menschlichen Granulationsgewebes*, Beitr z path Anat u z allg Path (Ziegler's) 1913, lvi, 346

3 Poscharisky, J. *Zur Frage des Fettgehaltes der Milz*, Beitrage, z path Anat u z allg Path, 1912, liv, 369

4 Kusunoki, Masanobu. *Lipoidsubstanzen in der Milz und im Lichenblut*, Beitr z path Anat u z Allg Path, 1914, lix

5 Gaucher. *De l'épithélioma primitif de la rate*, Paris, 1882

epithelial in origin. Since then about eighteen additional cases, confirmed by histologic examination, have been reported, resulting in considerable discussion and dispute over the origin of the large pale cells.

Marchand<sup>6</sup> was the first to note the presence of a peculiar homogeneous substance within the cells which is dissolved in alcohol, thus explaining the vacuolated appearance of the cells in the paraffin sections. Further, he concludes that there is "involved, therefore, not a real protoplasmic hyperplasia or even a tumor growth, but in the main a deposit of a foreign substance which, under certain treatment, leaves behind a vacuolated meshwork."<sup>7</sup>

Risel<sup>8</sup> studied the same case and confirmed Marchand's findings.

The next advance was made by Schultze<sup>9</sup> in his report of a case of diabetic lipoidemia associated with marked "Lipoidzellenhyperplasie" of the spleen with almost complete replacement of the pulp by these large pale cells. He pointed out that the vacuolated appearance of the cytoplasm was due to a deposition of a homogeneous substance of a lipoid character, probably closely related to cholesterol. After examination of material from Risel's and Schlagenhauser's cases he came to the conclusion that "in my case the same cells are concerned as in the case of Risel and Schlagenhauser. They agree in size and in staining reaction to embedded material."<sup>10</sup> While the cells were alike he did not attempt to identify the two conditions as from the same process, but suggested that, in Gaucher's disease, the vacuolated cytoplasm of the cells was also due to the deposition of lipoid substances. In his case he concluded that the cells were transformed reticular cells.

In his report of two cases of large-celled hyperplasia of the spleen pulp (*grosszellige Hyperplasie der Milzpulpa*) in diabetic lipemia, Lutz<sup>11</sup> showed that his cases are identical with Schultze's case, the cells

6 Marchand. Ueber sogenannten idiopathische Splenomegalie (Typus Gaucher), München med Wchnschr, 1907, liv, 1102.

7 Also nicht um eine eigentliche protoplasmatische Hyperplasie, noch weniger um eine Geschwulstbildung, sondern in der Hauptsache um Einlagerung einer fremdartigen Substanz zu handeln, die bei gewissen Behandlungen ein vakuolares Maschenwerk zurücklasst.

8 Risel, W. Ueber die grosszellige Splenomegalie (Typus Gaucher), Beitr z path u z allg Path, 1907, xlii, 241.

9 Schultze, W. H. Ueber grosszellige Hyperplasie der Milz bei Lipidaemie (Lipoidzellenhyperplasie), Verhandl d deutsch pathol Gesellsch, xv, Tagung 1912, xv.

10 Dass es sich bei meinem Falle um die gleichen Zellen wie dort handelt. Sie stimmen in der Grosse und dem Farberischen Verhalten an eingebettetem Material überein.

11 Lutz, Wilhelm. Ueber grosszellige Hyperplasie der Milzpulpa bei diabetischer Lipamie, Beitr z path Anat u z allg Path, 1914, lvi, 273.



being filled with lipoid substances. He also studied the material from the cases of Gaucher's disease reported by Risel, Schlagenhauser and by DeJong and von Heukelom, and confirmed Schultze in his conclusion that, with a few minor exceptions, the large pale cells were identical in the two conditions and contained deposits of lipoid material, but he pointed out that the identity of the cells does not imply that the processes are identical. He also noted three types of lipoid cells, each reacting slightly differently to the microchemical reactions for lipoids and fats, and only one containing an anisotropic substance. Most of the cells contained only isotropic material. This would indicate that the lipoid substances are not identical. He believed that the lipoids resulted from the transformation of fats deposited in the reticular and endothelial cells.

Mandelbaum and Brill<sup>12</sup> failed to obtain any positive reaction for neutral fat, cholesterol or cholesterol ester in the fresh material from a case (Bernstein's) of Gaucher's disease, but their report on this case has not been completed.

In the past year Sapegno<sup>13</sup> reported two cases of Gaucher's disease in which he concluded that there was a deposit of lipoids in the characteristic large pale cells, which the author considered as transformed embryonic lymphoid cells. He noted the similarity of Gaucher's disease and the cases of lipoidemia with large accumulations of lipoid cells in the spleen, but pointed out that this did not insure the identity of the two conditions. He referred to Kramer's case of obstructive jaundice in which masses of lipoid cells were described in Glisson's capsule of the liver and in the splenic trabeculae, and he criticized Aschoff's classification of these allied conditions under xanthelasmic diseases in three divisions, as being premature and artificial. He suggested the following classification of xanthelasmic diseases as a temporary one until more is found out about these processes:

- (a) Lipoid infiltration of specific elements (Gaucher's disease)
- (b) Lipoid infiltration of the cells of the reticulum and endothelium (Schultze-Lutz type)
- (c) Lipoid infiltration of purely connective tissue elements (Kramer)

Anitschkow<sup>14</sup> has produced experimentally, in rabbits, a condition similar to Gaucher's disease by prolonged feeding of cholesterol, in

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12 Brill, N. E., and Mandelbaum, F. S. Large Cell Splenomegaly (Gaucher's Disease), *Am Jour Med Sc*, 1913, cxlvi, 863.

13 Sapegno. La Spenomegalia tipo Gaucher e la Splenomegalia lipoidemica, *La Pedriatica*, xxii, 606.

14 Anitschkow. Ueber experimentelle erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, *Beitr z path Anat u z allg Path*, 1914, lvii, 201.

that the parenchyma of the spleen, lymph nodes and bone marrow is replaced by large pale vacuolated cells containing large deposits of cholesterol ester. The picture in the spleen resembles very closely that described by Schultze and Lutz. The latter noted this close similarity. The deposit occurs in the endothelial and reticular cells. While Anitschkow noted the resemblance to Gaucher's disease, he believed that, at present, a complete analogy is not warranted, though there is a systemic involvement in the rabbits, in that all organs involved are provided with those cell elements (reticular cells, endothelial cells, Kupfer cells, etc.) which have essentially the same functional significance.

The case<sup>15</sup> on which our study is based is that of an infant 11 months of age, with a clinical picture which, in general, simulated Gaucher's disease. In many respects it bore a close resemblance to Niemann's case<sup>16</sup>. The spleen, liver and lymph nodes presented the usual changes, but the unusual feature of the case was the almost complete substitution of the medulla of both suprarenals by clusters of the large pale vacuolated cells. The latter were also present in Peyer's patches, in the intestines and in the thymus, besides involving the adventitia of some of the smaller vessels. The process was thus much more diffused than in any case hitherto described, and also the first one described in an infant, when the condition may be more diffused than when it occurs in adults.

#### MICROCHEMICAL STUDY

Examination of frozen sections of the fresh tissue and of tissue fixed in liquor formaldehydi showed the presence of many small homogeneous droplets in the cytoplasm of most of the cells, giving it a coarsely granular appearance under low magnification. These droplets disappeared on treatment with alcohol or ether, leaving the vacuoles which are so prominent in the paraffin and celloidin sections. A large number of the cells did not show these droplets, or else they were so small that they appeared as small granules. Acids and alkalis had no effect on the droplets. With the polarized light, many of the cells in the spleen had a luminous appearance with here and there a small highly refractile granule. In addition, there were small clusters of cells which, in the spleen, tended to group in and about the malpighian bodies, and which contained a large number of anisotropic droplets, some of the larger ones showing dark crosses in the center.

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15 A detailed report of this case, associated with that of the sister of our patient, will be published shortly in the Bulletin of Johns Hopkins Hospital.

16 Niemann. Ein unbekanntes Bild der Kinder, Jahrb. d. Kinderh., 1914, lxxix, 1.

Some of the smaller ones were needle-shaped. On warming, most of these doubly refractile substances either became very obscure or entirely disappeared, and reappeared on cooling. While most of these bodies were within the large pale cells, some were found between them. While cells with isotropic droplets in the cytoplasm greatly predominated in the spleen and liver, cells containing anisotropic droplets were more abundant and more diffusely distributed in the lymph nodes and, especially, in the medulla of the suprarenal gland. This reaction toward the polarized light would indicate the presence of cholesterol or one of its compounds,<sup>17</sup> but the Golodetz reaction for

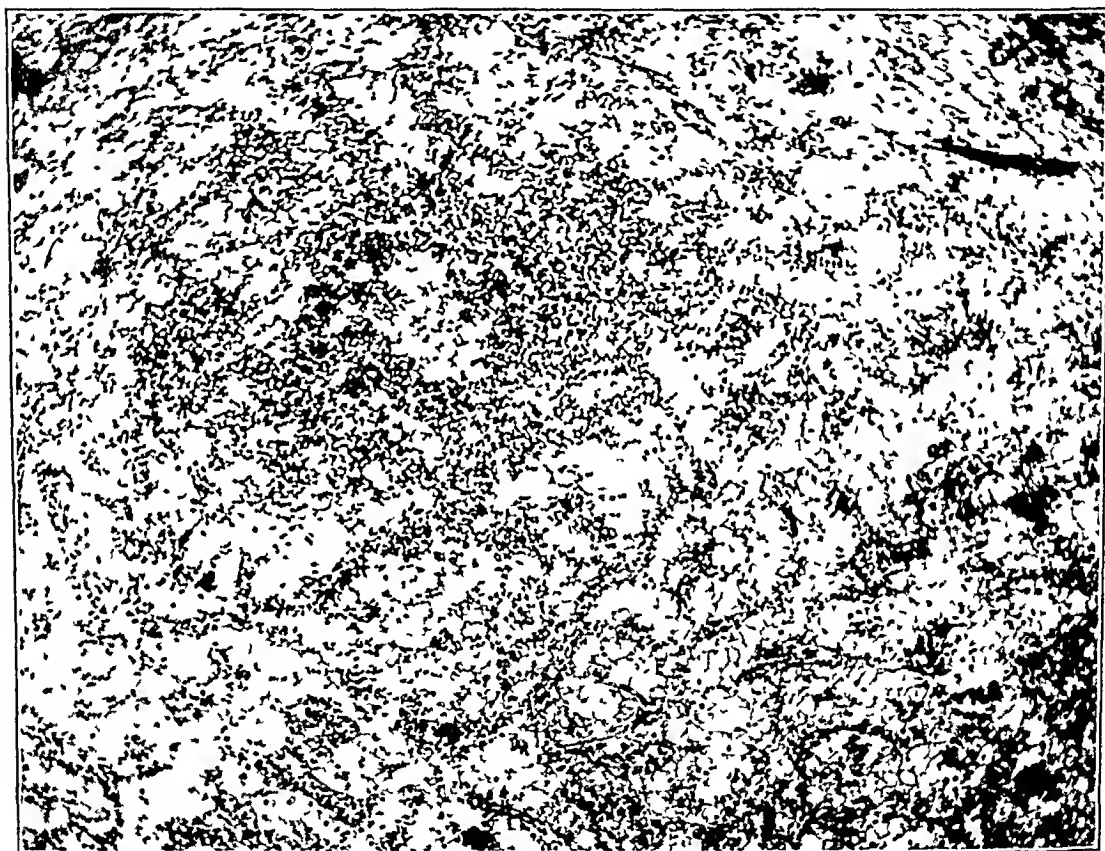


Fig 1—Photomicrograph of the spleen,  $\times 85$ , stained with iron hematoxylin, showing the more or less extensive replacement of the spleen pulp by the distinctive large pale cells. Note that some of the cells are also present in the center of a malpighian body.

cholesterol was negative. Scharlach R and sudan III stained the large pale cells a faint orange or not at all, whereas the neutral fat in control sections took a deep orange-red. With osmic acid the cells took a very faint gray. With nilblau sulphate the droplets in the cytoplasm

<sup>17</sup> Aschoff. Zur Morphologie der lipoiden Substanzen, Beitr. z. path. Anat. u. z. allg. Path., 1910, xlvii, 1.

of the distinctive large cells in the spleen and liver stained from a violet to a pale blue. In one section of the spleen a faint pink was obtained. In the lymph nodes the color was either violet or pink. In the medulla of the suprarenal glands a definite pink was invariably obtained. The droplets in the cortex stained violet or blue. Weigert's hematoxylin (Schultze<sup>9</sup>) showed deep blue droplets in the large pale cells. Lorain-Smith-Dietrich's stain for lipoids was also positive in most of the large cells. Weigert's myelin sheath stain was only partly positive in that the droplets were not entirely decolorized. The material did not stain with neutral red, or with trypanblau or trypanrot. Fischler's stain for fatty acids and soaps was negative. With Ciaccio's stain the results were at first negative, but after the time in chrome salts had been increased and after preliminary treatment with Carlsbad salt, in accordance with Kasarinoff's suggestions,<sup>18</sup> faint but very definite pale orange droplets appeared in the large pale cells in the spleen. This would indicate the presence of lecithin (Ciaccio<sup>19</sup>), but it is more probable that other lipoids are equally responsible for the reaction (Polosow<sup>20</sup>).

The foregoing microchemical reactions are not entirely satisfactory, being incomplete or poorly defined in some cases. Very little neutral fat is present. The anisotropic reaction and pink color in the suprarenal medulla and some parts of the spleen indicate the presence of cholesterol or one of its compounds, while the isotropic material and the violet or pale blue color with nilblau implies the presence of other lipoids such as lecithin and phosphatids. The variation and incompleteness of the other reactions is accounted for, in part, by the probable presence of several different lipoid substances and, in part, to alterations produced by the formaldehyd fixation, since all of the material at hand was fixed in 10 per cent dilution of liquor formaldehydi. Both Bell<sup>21</sup> and Bullard<sup>22</sup> have shown that liquor formaldehydi materially interferes with the reactions for lipoids. On the other hand, Kasarinoff<sup>18</sup> showed that preliminary treatment of formaldehyd-fixed tissue in Carlsbad salt renders the lipoids more susceptible to the lipoid stains, and we noted the same improvement in following this suggestion. Risel and Marchand did not note any

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18 Kasarinoff. *Vergleichungen zur Histologie der Lipoide*, 1910, xlix, 490.

19 Ciaccio, Carmelo. *Ueber das Vorkommen von Lecithin in den zellularen Entzündungsprodukten und über besondere lipoidbildende Zellen (Lecithinzellen)*, *Zentralbl f allg Path u path Anat*, 1909, p 385.

20 Polosow, A. A. *Zur Morphologie der Lipoidsubstanzen*, *Zentralbl f allg Path u path Anat*, 1910, p 1014.

21 Bell, E. T. *Staining of Fats in Epithelial Cells and Muscle Fibers*, *Anat Rec*, 1910, iv.

22 Bullard, H. Hays. *The Microscopical Demonstration of Fats in Tissue Sections*, *Jour Med Research*, 1913, xxvii, 55.

change in the material in the cells of their cases as a result of fixation. In our case the presence of many isotropic droplets in the cells and comparatively few anisotropic droplets may be the result of the transformation of the latter into the former by the action of liquor formaldehydi, as was shown by Dunin-Karwicka<sup>22</sup> and Aschoff<sup>17</sup>.

These liquid crystals and other anisotropic particles are undoubtedly cholesterol or some derivative (Aschoff,<sup>17</sup> Dunin-Karwicka,<sup>23</sup>

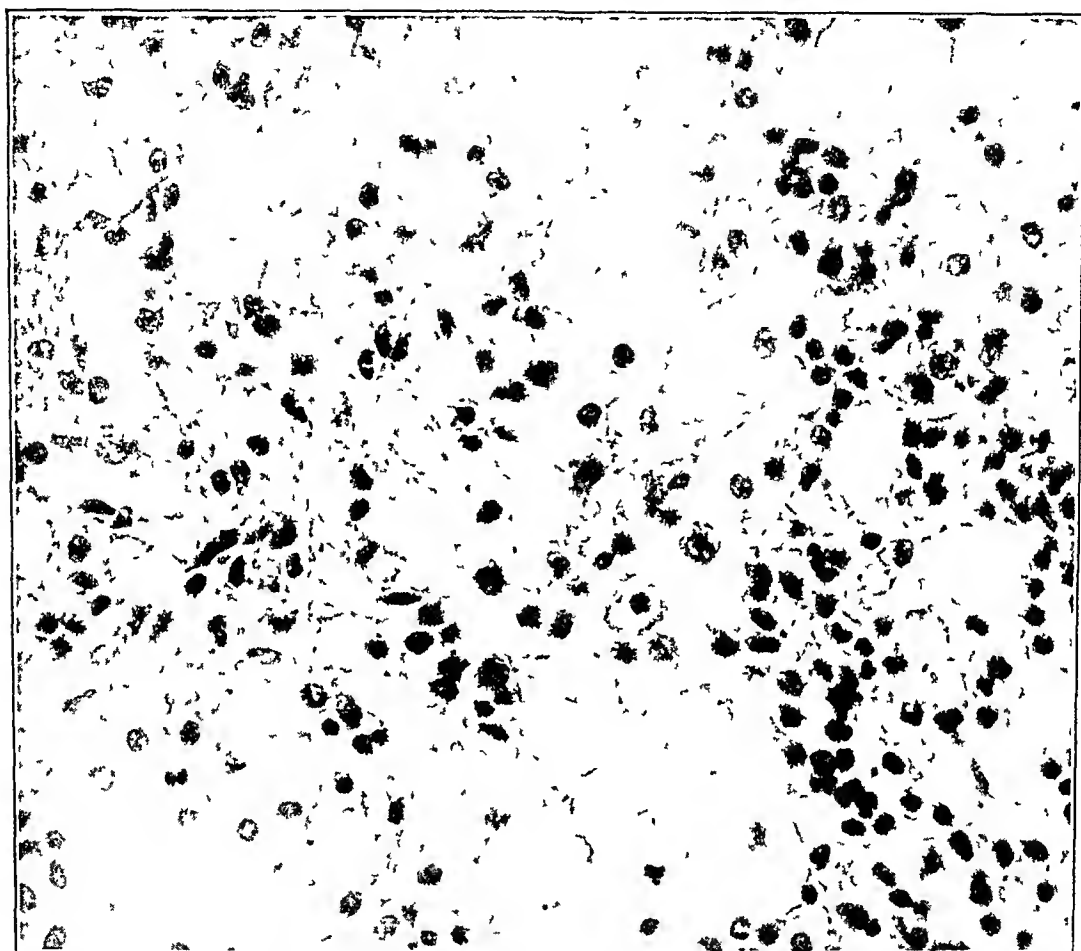


Fig 2—Photomicrograph from the same areas as in Figure 1, but with a magnification of 450, showing the character of the large cells and the vacuoles that are present in the cytoplasm.

Chalatow<sup>24</sup>) Most of the cells did not contain anisotropic particles, but Aschoff<sup>17</sup> pointed out that the absence of doubly refractile substances does not exclude cholesterol. The predominance of violet or

23 Dunin-Karwicka. Ueber das physikalische Verhalten und das physiologische Vorkommen der doppeltbrechenden Lipoide, Beitr z path Anat u z allg Path, 1911, L, 437.

24 Chaladow. Ueber Myelinosis und Xanthomatosis, Virchows Archiv f path Anat, 1914, ccxvii, ueber flussige Kristalle in tierischen Organismus, Frankfurt Ztschr f Pathol, 1913, xiii, 189.

pale blue cells over the pink ones with nilblau is one point that would suggest a corresponding predominance of lecithin and phosphatids over cholesterol. Even at best, the staining reactions are notoriously unreliable for careful differentiation of the various lipoids and fats and, in formaldehyd-fixed tissue, this defect would be enhanced. However, the conclusion that is justified from the histochemical study of the tissue is that the material, accumulated in the large pale cells, is not a protein or a neutral fat, but is composed of fatlike bodies—lipoids, including cholesterol and lecithin. The relative amount of cholesterol as compared to lecithin and the phosphatids is uncertain.

Owing to the unreliability of the fat and lipid stains in the differentiation of the lipins, it occurred to us that more definite information about the material accumulated in the large pale cells could be obtained by extracting the liver and spleen for lipoids, quantitatively. The great difficulty with this procedure is again the fact that all of the material at our disposal had been fixed in liquor formaldehydi, and it is well known that lipoids and even neutral fats are more or less altered by this solution. However, the extent of this alteration, quantitatively, has not, to our knowledge, been determined, and it was suggested that if the same technic was carried throughout with proper control organs and Gaucher organs, a general conception of the main changes in the distribution and relation of the lipins in Gaucher's disease may still be obtained.

The quantitative method for the determination of lipoids used was one elaborated in accordance with the suggestions of Frankel<sup>25</sup> and Erlandson,<sup>26</sup> and depended on the initial extraction with petroleum benzin followed by extraction with alcohol. The technic and method were identically the same for all determinations and were briefly as follows:

The organs used were the spleen and liver. Extraction was made only from the dried tissue. *A* The tissue was first extracted in a Soxhlet extractor and reflux condenser for thirty-six hours with petroleum benzin of a low boiling point (less than 37 C). This removed practically all of the fat and lecithin and a large part of the cholesterol and phosphatids. *B* The tissue was then extracted thirty-six hours with hot 95 per cent alcohol. This extract contains a part of the cholesterol and phosphatids. By means of saponification with alcoholic sodium hydroxid, the phosphatids were mostly saponified, and the residue of unsaponified material consisted chiefly if not entirely of cholesterol. *C* The petroleum benzin extract was treated with a large amount of cold acetone. The precipitate of acetone-insoluble material is probably composed mainly, if not entirely, of lecithin. *D* The filtrate from *C*, which contained all of the

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25 Frankel, Sigmund. Darstellung von Lipoiden aus Gehirn und anderen Geweben. Abderhalden. Handbuch der biochemischen Arbeitsmethoden, 1911, v.

26 Erlandson, cited by Bang, Ivar. Chemie und Biochemie der Lipoidsubstanzen, Wiesbaden, 1911.

fixed fat and a part of the cholesterol and phosphatids, was evaporated to a small volume and 95 per cent alcohol added in excess. The fixed fat is not dissolved, while the cholesterol and phosphatids go readily into solution. *E* The amount of fixed or neutral fat in *D* is obtained by saponification. *F* The filtrate from *D*, that is, the phosphatids and cholesterol, was saponified and the cholesterol roughly separated from the phosphatids as it cannot be saponified. These quantities were then added to similar quantities in *B*. *G* The lecithin or acetone-insoluble material was redissolved in ether, the solvent evaporated, the residue dried to a constant weight and then saponified to check the result found gravimetrically. In each of the foregoing steps the solvent was evaporated spontaneously, and the residue dried in a desiccator to a constant weight.

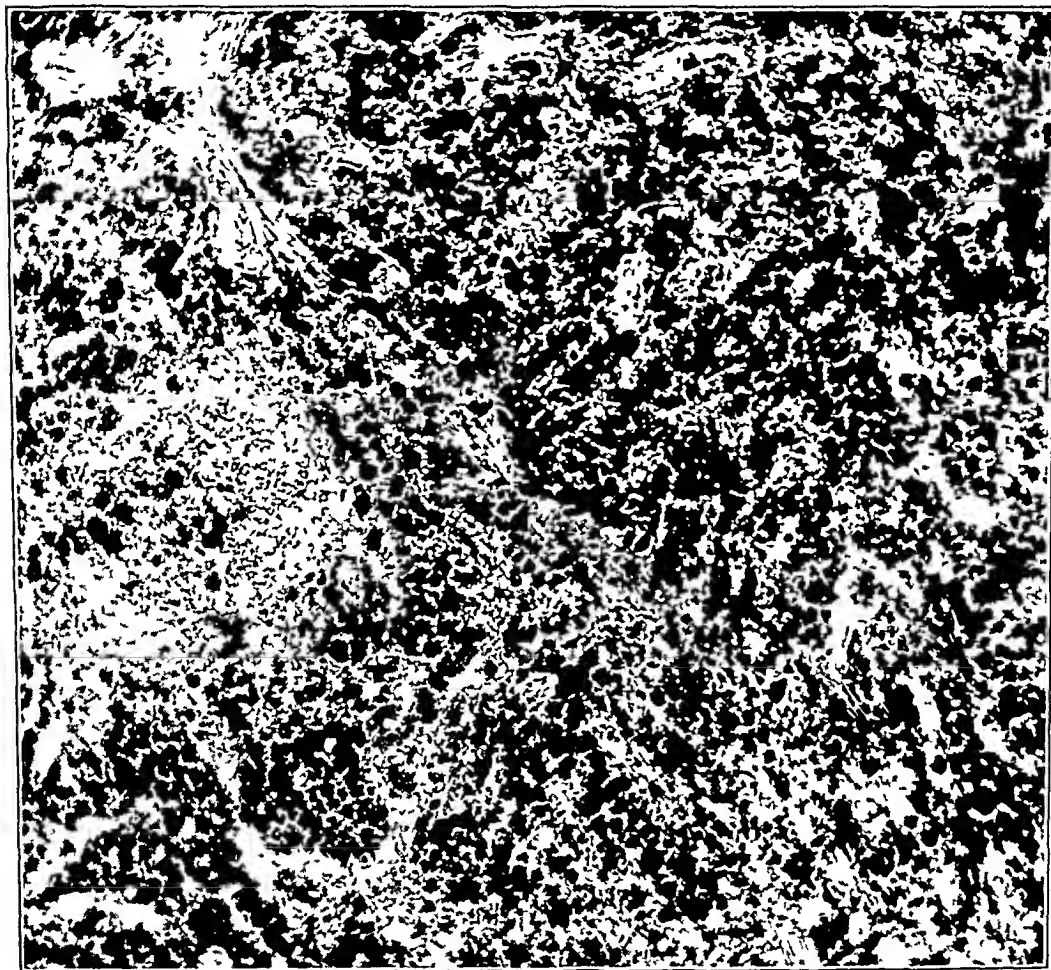


Fig 3—Photomicrograph of a preparation,  $\times 85$ , stained for lipoid material after Schultze's chrome hematoxylin method. The large pale cells are represented by irregular rounded black masses owing to their being filled with lipoid material, which takes a deep steel-blue color.

and the weight recorded. The saponification was not made in all of the determinations, it being considered unnecessary, inasmuch as it only afforded a check on the gravimetric values.

This method is not perfect, but the errors that occur are common to both the Gaucher tissue determinations and those on the control organs. For controls, fresh tissue from the spleens and livers,



Organs	Determination	Total Weight of Material, Gm	Terms	(Acetone-Insoluble Portion)		Alcohol Soluble Portion of Acetone Filtrate			Direct Alcoholic Tissue Extract			Total			Fats (fixed)	Total Lipins
				By Precipitation	By Saponification	Total	Saponifiable (Lecithin, Phosphatids, etc.)	Non-saponifiable (mostly Cholesterol)	Total	Saponifiable (Lecithin, Phosphatids, etc.)	Non-saponifiable (mostly Cholesterol)	Grand Total				
Normal spleen	Case 1	3 617	{ Grams } Per cent	0715 1 97		2544 7	2515 6 94	0029 06	2934 8 11	2934 8 11	0 0	5449 15 05	0029 08	5478 15 13	1644 4 5	7837 21 55
	Case 2	2 091	{ Grams } Per cent	061 2 9		193 9 23			316 15 12	1 93 9 23	123 5 9	? ?	? ?	509 24 3	006 3	576 27 5
	Case 3	4 26	{ Grams } Per cent	147 3 45		1845 4 33			347 8 14			? ?	? ?	5315 12 47	022 52	7005 16 44
	Average		Per cent	2 77		6 85			10 45					17 30	1 77	21 84
Gaucher spleen	Det 1	2 418	{ Grams } Per cent	355 14 3	255 10 2	3588 13 2	2032 8 16	1256 5 06	Lost Lost	Lost Lost	Lost Lost	2032 8 16	1256 5 06+	3288 13 2+	0066 26	7498+ 27 76+
	Det 2	2 717	{ Grams } Per cent	2246 8 43		5229 19 3	214 8	3089 11 3	632 23 3	384 14 16	248 8 14	598 22 16	556 19 44	1 154 41 6		1 378 50 03
	Det 3	1 792	{ Grams } Per cent	202 11 28	157 8 76	373 20 8	328 18 3	055 2 5	388 21 8	237 13 2	151 8 6	565 31 5	206 11 1	771 42 6	0229 1 2	996 54 08
	Average		Per cent	11 33	9 48	17 76	11 35	6 28	22 5	13 68	8 37		26 83	15 27	42 1	73
Normal liver	Case 1	5 00	{ Grams } Per cent	0824 1 64	0732 1 46	274 5 49	295 5 9	0 0	694 13 88	585 11 7	109 2 19	880 17 6	109 2 19	989 19 8	490 9 8	1 561 31 16
	Case 2	5 064	{ Grams } Per cent	177 3 5		225 4 45			443 8 75					668 13 2	0520 1 03	945 17 73
	Case 3	2 874	{ Grams } Per cent	48 2 01		236 8 2			293 10 2					529 18 4	084 2 74	661 23 15
	Average		Per cent	2 33		6 05			10 94					17 13	4 52	24 03
Gaucher liver	Det 1	2 8274	{ Grams } Per cent	2357 10 11		435 18 6	2139 9 2	2213 9 5	1194 5 12					5544 23 22	002 09	782 33 9
	Det 2	4 906	{ Grams } Per cent	550 11 21	248 5 05	8505 17 33	38 7 75	47 9 37	488 9 94	2 4 08	288 5 87	58 11 83	758 15 24	1 338 27 07	09 2	1 978 40 48
	Average		Per cent	10 66	5 05	17 96	8 97	9 43	9 94	4 08	5 87	11 83	15 24	27 07	1 04	37 19

Note.—Through the kindness of Drs J H Mason Knox and of H O Schmeisser of Baltimore, material from an infant sister of our patient with a very similar history and pathologic nature was placed at our disposal.



obtained at random from the necropsy room, were used. Inasmuch as no complete quantitative analysis of the different lipoids in the normal human spleen or liver has been published to our knowledge, our determinations afford a general conception of their distribution and relation.

The results of the determinations are condensed in the accompanying tables. Table 1 includes the data of the determinations arranged so that those on the Gaucher material may be readily compared with those on the control tissue. From this table it is seen that there is a very striking uniform increase in the lecithin (or rather the acetone-insoluble residue) in the Gaucher material as compared with that in the control organs. There is from three to four times as much in the former as in the latter. For example, in the Gaucher spleen there is an average of 11.33 per cent of dried substance or 21 per cent of total lipins as compared to 2.77 per cent of dried substance and 12 per cent of total lipins for an average of three different spleens. For the livers the proportion of lecithin is still higher, being 26 per cent of the total lipins as compared to less than 10 per cent for normal livers. There is also a marked increase in the cholesterol in the Gaucher tissue, but our data on the normal material are not sufficiently complete on this point to make them reliable. The phosphatids do not show such a marked increase, while the fixed fats in the Gaucher tissue are markedly diminished. The total lipins are considerably increased (from 60 to 100 per cent), but not as much proportionately as the lecithin. The high fat content of the control spleen and liver of the first case is readily accounted for by the fact that these organs were taken from a case of pulmonary tuberculosis in which all of the abdominal viscera showed considerable fatty change.

Table 2 shows the result of a series of determinations made to show the effect of liquor formaldehydi on the extraction of lipoids and fats after our method. These determinations were made on the fresh tissue and formaldehyd-fixed material of the same cases which were as near normal and as near the age of our case of Gaucher's disease as we could obtain. The data are arranged together so that a comparison between the unfixed and formaldehyd-fixed tissue may be readily made. It is at once evident from this table that while liquor formaldehydi does cause some alteration, it is so small that it is practically negligible when compared with striking changes as are present in the Gaucher tissue. Throughout this series of determinations, the values for the formaldehyd-fixed tissue are slightly higher than for the unfixed material. This may be explained by either the liberation of some fats firmly bound in protein combination by liquor formaldehydi or, more probably, by the addition of a formol radical to the lipoid substances. It is well known that with lecithin this combination occurs, and it would

TABLE 2—LIPIDS IN FRESH MATERIAL AND MATERIAL FIXED IN LIQUOR FORMALDEHYDI

	Spleen					Liver				
	Fresh Tissue		Aver age	Tissue Fixed in Liquor Formaldehyd		Aver age	Fresh Tissue	Tissue Fixed in Liquor Formaldehyd		Aver age
				3 mo	2 mo			3 mo	2 mo	
Case	1558	1563		1558	1563		1558	1558	1563	
Amount of dried material	1 498	2 523		1 225	1 892		2 874	1 328	1 889	
Lecithin (Ppt by acetone)	020	055		018	044		058	033	040	
	1 33	2 17	1 76	1 46	2 32	1 89	2 01	2 48	2 11	2 28
Cholesterol, phos phatids, etc	027	189		100	115		236	114	169	
	1 8	7 4	7 4	8 16	6 08	7 12	8 2	8 6	8 9	8 75
	159	225		129	1 43		293	184	237	
	10 6	8 9	9 7	10 5	8 09	9 28	10 2	13 9	12 5	13 2
	186	414		229	258		529	298	406	
	12 4	16 3	14 3	18 66	14 17	16 41	18 4	22 5	21 4	21 95
Fixed fats (saponifiable)	0141	0772		0187	096		0845	0376	095	
	93	3 05	1 99	1 5	4 77	3 13	2 74	2 82	4 2	3 51
Total lipins	220	546		265	398		6715	368	541	
	14 66	21 42	13 02	21 62	21 26	21 44	23 15	27 80	27 71	27 76

account for the slightly increased amount of lecithin obtained in our determinations. It is only in the case of fixed fats that the change is very considerable.

In Table 3 the results of our determinations are summarized in terms of percentages so that they are more easily interpreted. Inasmuch as the Gaucher tissue was fixed in liquor formaldehydi there is, in this table, also a series of determinations on two formaldehyd-fixed controls for comparison. This table shows that the combined total of cholesterol and phosphatids in the Gaucher spleen is markedly increased over that in the control spleens, while in the liver the increase was not nearly so prominent. Their percentage of the total lipins is not materially changed. The lecithin again shows a very striking increase in both organs in Gaucher's disease, as shown in Table 1, while the fixed fat is decreased.

The results of this quantitative analysis lead us to conclude that there is a very marked alteration in the relation and distribution of the lipins in our case of Gaucher's disease, and that there is a striking increase in the acetone-insoluble material (which is most probably lecithin and lecithin-like bodies), a marked accumulation of cholesterol or one of its compounds, a relative diminution in the phosphatids and a very considerable decrease in the quantity of fixed fats. They also show that, exclusive of the fixed fats, the alteration of the lipins produced by formaldehyd fixation does not materially interfere with their extraction, but owing to the paucity of our determinations not much stress can be placed on this point.

#### SUMMARY AND COMMENT

The microchemical study of our case indicates not only the accumulation of lipoids in the large pale cells but also that these bodies are not identical. Many of the cells contain droplets that give reactions for cholesterin ester, that is, were doubly refractile to polarized light, stained pale orange with sudan III and pink with nilblau sulphate. Other cells appeared as if covered with a luminous dust which Chaladow<sup>24</sup> showed was due to the accumulation of very small liquid crystals. These are formed wherever fat is present from the union of fatty acid and cholesterol<sup>24</sup>. However, most of the cells did not show anisotropic particles, and gave a violet or pale blue color with nilblau, a faintly positive reaction for Ciaccio's stain, a positive reaction for the Lorain-Smith-Dietrich reaction for lipoids and also for myelin, suggesting the presence of other lipid bodies. The fact that formaldehyd fixation may, especially if prolonged, interfere with the various microchemical reactions for lipoids and with the action of polarized light makes the interpretation of the results of these methods on for-

TABLE 3—COMPARATIVE TABLE OF LIPOID PERCENTAGES IN CONTROL AND GAUCHER ORGANS

Description, Clinical and Pathologic	Fresh Tissue						Formaldehyd Tissue				Gaucher Tissue Fixed in Liquor Formaldehyd				Aver age Per- centage of Total Lipins
	Man, Age 40 yrs Marked Fatty Degen- eration of Viscera (Tuber- culosis)	Child, Age 2 yrs Menin- gitis	Child, Age 7 yrs Scarlet Fever	Child, Age 11 mos Menin- gitis, Aut 1553	Child, Age 1 yr Pneu- monia, Aut 1563	Aver- age Per- centage of Total Lipins	Aut 1558	Aut 1563	Aver- age	Aver age Per- centage of Total Lipins	First Deter- mina- tion	Second Deter- mina- tion	Third Deter- mina- tion	Aver age	
Spleen															
Acetone - insoluble ppt (Lecithin)	1 97	2 9	3 45	1 33	2 17	2 32	11 2	1 46	2 32	1 89	14 3	8 43	11 28	11 33	20 7
Cholesterol and phos- phatids	15 13	24 3	12 47	12 4*	16 3	16 08	78	18 66	14 17	16 4	13 2*	41 6	42 4	42	77 7
Fat (fixed)	4 5	3	52	93	3 05	1 86	9	1 5	4 77	3 14	26	?	1 2	73	1 3
Total Lipins	21 9	27 5	16 44	14 66	21 42	20 51		21 62	21 26	21 44	27 57*	50 03+	54 8	54 06	
Liver															
Acetone - insoluble ppt (Lecithin)	1 64	3 5		2 01	3 5	2 66	11 5	2 48	2 11	2 28	10 11	11 21		10 66	28 6
Cholesterol and phos- phatids	19 8	13 2		18 4	12 4*	15 95	69 0	22 5	21 4	21 95	23 72*	27 07		25 49	68 2
Fat (fixed)	9 8	1 03		2 74	?	4 37	19	2 82	4 2	3 51	09	?		1 04	2 8
Total Lipins	31 2	17 73		23 15	15 9+	22 99		27 8	27 71	27 77	33 9+	40 48		37 19	

\* Some lost

maldehyd material uncertain. A positive result would be of much more value than a negative one, and the absence of anisotropic droplets, for example, in most of the cells may be interpreted either as indicating an alteration produced by liquor formaldehydi or the presence of other lipid bodies that are isotropic. It may be for this reason that Lutz<sup>11</sup> found the Lorain-Smith-Dietrich stain for lipoids in the formaldehyd-fixed material of Risel's and of Schlagenhauser's cases negative, whereas Schultze,<sup>9</sup> who apparently examined the material about two years earlier, when it was fresher, found the reaction positive. The microchemical reactions in our case are practically identical with those described by Lutz<sup>11</sup> in his first case and very similar to those of

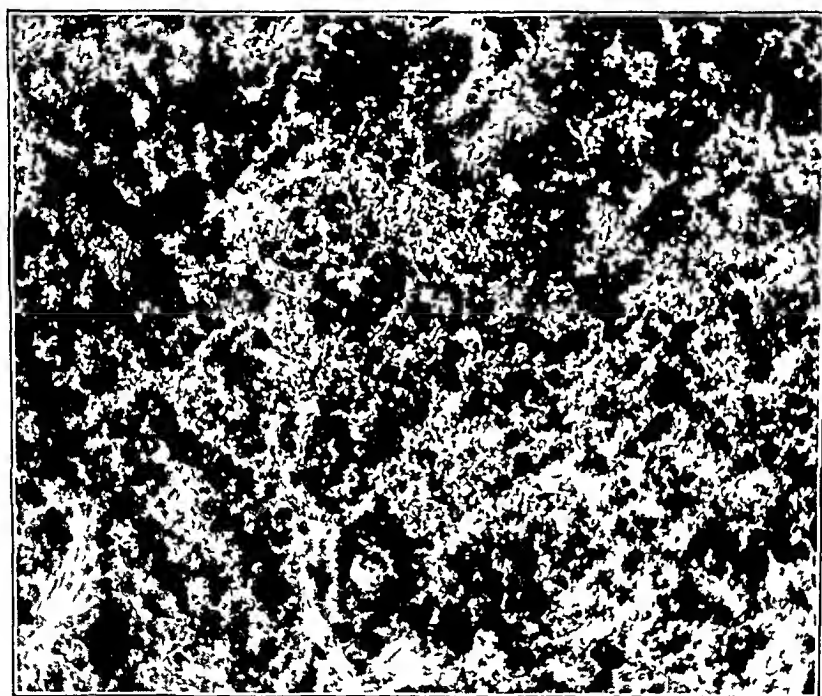


Fig. 4—Photomicrograph of a preparation,  $\times 85$ , stained for lipoids after Lorain-Smith-Dietrich's method. The distinctive large pale cells are more or less filled with lipoid substances and stand out as irregular round black masses.

Schultze.<sup>9</sup> Both of these authors examined the material of the Risel and Schlagenhauser cases and concurred in the identity of the cells and the lipid character of the intracellular droplets of their cases and the cases of Gaucher's disease. Sapegno<sup>13</sup> also noted the same lipid infiltration in the cells of his case of Gaucher's disease, but asserted that the cells were of lymphocytic origin and not endothelial and reticular as the other authors contended.

There is no question about the identity of the cells and the lipid character of the material accumulated in our cases with the foregoing cases of Gaucher's disease and of "grosszellige Hyperplasie der Milz."

This does not imply that the lipoids are identical. They are so complicated and difficult to separate that conflicting results with the crude microchemical reactions are not at all surprising, and no attempt to separate these cases on the basis of slight variations in their reactions to our present unreliable microchemical reactions would be warranted.

The quantitative determination of the lipoids is equally difficult and uncertain (Bang<sup>26</sup>), but for our purposes it serves in a general way to confirm the conclusions, based on the microchemical reactions, that there is a great increase in lipoids with the Gaucher liver and spleen and that lipoids, such as lecithin-like bodies as well as cholesterol compounds, are mainly responsible. In this way the question as to whether the negative reaction of most of the large cells to cholesterol is due to alterations produced by formaldehyd fixation or to the presence of different lipid bodies is definitely determined. We have not found any complete quantitative analysis of the different lipoids and fats in the spleen. Wells<sup>27</sup> shows that the dried normal spleen contains 14.2 per cent lipins, a figure that is somewhat lower than our determinations for the control spleens, though in one case (Table 3) the figure of 14.66 per cent was very close. Our higher average is probably due to our material being mostly pathologic. In the normal liver<sup>27</sup> the lipin content amounts to 5 per cent of the moist weight or about 22 per cent of the dried weight, but in pathologic organs the lipins may run up as high as 75 per cent of the dried weight. According to Rumpf,<sup>28</sup> the fat (total lipin) content of the liver varies from 2 to 56 per cent of the dried weight with an average of 19.6 per cent, and the content of the spleen varies from 1.4 to 24.8 per cent, with an average of 9.96 per cent. His figures for the liver correspond closely with our determinations, but those for the spleen are much lower. No determination of the different lipoids was available. Aschoff<sup>17</sup> showed that cholesterol formed 5.9 per cent of the normal liver cell. Our determinations give a general conception of the distribution and relation of the main lipoids and fats in the average organ obtained at necropsy, but the number of cases analyzed is too few to make the results very reliable. The findings would also indicate that liquor formaldehydi does not interfere so extensively with the extractibility of lipoids and fats, but that a good working conception may be obtained of their amount and should encourage similar determinations to be made on this and other rare and interesting xanthelasmic tissues, of which usually nothing but formaldehyd-fixed material is available. From the microchemical reac-

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27 Wells, H. Gideon. *Chemical Pathology*, Philadelphia, W. B. Saunders & Company, 1914, p. 495.

28 Rumpf. Ueber den Fettgehalt des Blutes und einigen Organe des Menschen, *Virchows Archiv f. path. Anat.*, 1903, clxxiv, 163.

tions it is very probable that the lipid substances, especially a lecithin-like body and cholesterol that are quantitatively greatly increased in the liver and spleen as a whole, are accumulated in the droplets within the large pale cells

The nature of the process which underlies this peculiar accumulation of lipoids opens up a broad field for speculation. The individual large pale cells in Gaucher's disease are not specific for this disease. They occur not only in Gaucher's disease and in allied conditions, such as Schultze's case of lipoidemia, but also in various more common pathologic lesions such as chronic granulation tissue<sup>2</sup> and chronic pyometra and pyosalpingitis. They have even been noted free in the

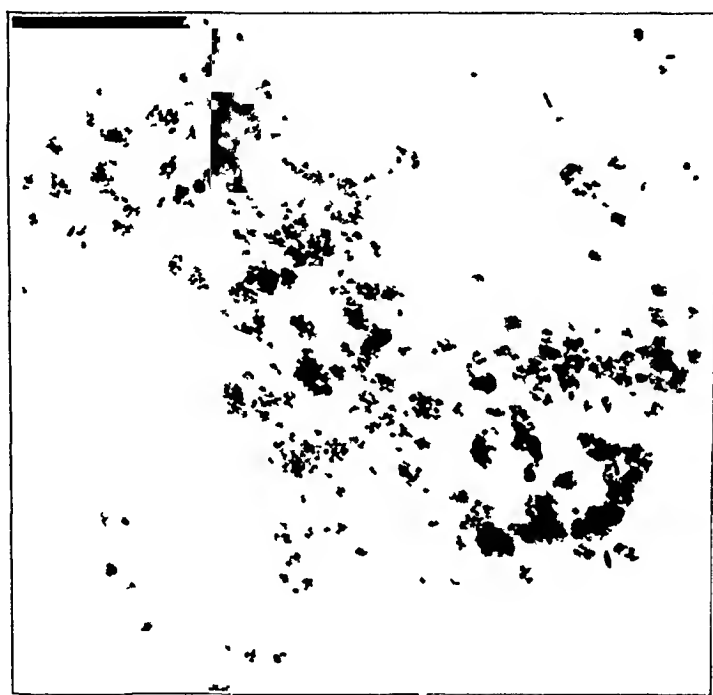


Fig 5—Photomicrograph of a frozen section,  $\times 160$ , through a polarizing microscope showing the doubly refractile liquid crystals in many of the large pale cells. Note that this anisotropic material is much more abundant in some cells than in others.

blood stream (Kawamura<sup>29</sup>). Whether or not they occur in the blood in Gaucher's disease has not been reported, largely, perhaps, because no careful search was made for them. They do not necessarily represent a degenerative or a pathologic process, for Ciaccio<sup>30</sup> and Kusunoki<sup>4</sup> have noted them in normal conditions, the former as "Lecithin-

<sup>29</sup> Kawamura. Cholesterinesterverfettung, Jena, Fischer, 1911.

<sup>30</sup> Ciaccio, Carmelo, Beitrag zum Studium der Zelllipoiden in normalen und pathologischen Verhältnissen und einer besonderen Entartung von Lipoid Typus (Lecithinische Entartung), Zentralbl f allg Pathol u path Anat, 1909, xx, 771.

zellen" in the blood-forming tissues, and the latter as "lipoid" cells in the spleen. They both point out that they have the physiologic functions of absorbing and disposing of lipid substances in the tissues, and that in pathologic conditions these cells may accumulate in great numbers. Chalutow<sup>24</sup> termed this accumulation of lipid material "xanthomatosis" or "myelinosis," according as the material accumulated in the supporting tissue of the organs or in the parenchyma, the former being an active process, the latter a passive one. Accordingly, he would call the spleen described by Lutz a case of xanthomatosis. Kusunoki<sup>4</sup> maintained that the lipid cells were mainly reticular cells, though some were derived from the endothelium of the lymph sinuses, and had the same origin as the pigmented cells of the spleen. Anitschkow<sup>14</sup> held that these lipoids were also present in the reticulo-endothelial cells of the bone marrow and lymph nodes and in the Kupfer cells of the liver, and that they took up carmin and other vital stains and iron pigment. He maintained that in his experimental rabbits the accumulation of cholesterol involved a certain system of cells, that is, the reticulo-endothelial cells of the spleen, bone marrow, lymph glands and the Kupfer cells of the liver, and suggested the analogy with Gaucher's disease, but refrained from asserting any identity between the two processes. Soper<sup>31</sup> pointed out recently that the spleen owes its part in cholesterol metabolism mainly to the large proportion of the reticulo-endothelial system of the body (designated by Landau<sup>32</sup> and Aschoff as the "endothelial Stoffwechsel Apparat or Milzapparat," which the latter hold plays the main rôle outside of the liver in the absorption, transformation and retention of cholesterol) which it occupies. It is this system which forms the lipid cells, which takes up the vital stains, which is concerned in the iron pigment metabolism and which is the seat of the striking changes in experimental cholesterol-steatosis following a prolonged cholesterol diet. Of the various conditions in which the lipid cells accumulate in large numbers, it is only in the experimental type produced in rabbits by excessive cholesterol feeding that one is justified in considering the lipid material as cholesterol to the exclusion of other lipoids and, even here, quantitative determinations should be made to confirm the more or less inadequate microchemical methods of recognizing the main lipid bodies. It is because of the inadequacy of microchemical methods and the close relation of one lipid to another that, in the cases of human xanthelasmic conditions, it would be hazardous to limit the lipoids to one par-

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31 Soper, W. B. Ueber Beziehungen der Milz zum Cholesterin-stoffwechsel, *Beitr z path Anat u z allg Path*, 1915, 1x, 233.

32 Landau, M., and McNee, J. W. Zur Physiologie des Cholesterin-stoffwechsels, *Beitr z path Anat u z allg Path*, 1914, lviii, 667.



ticular type Accordingly, we hesitate to speak of cholesterol infiltration, "cholesterinverfettung," etc., and prefer the more general term "lipoid" until more is known about lipoids and their recognition microchemically

In our case it is important to recall that the medulla of both suprarenal glands was almost replaced by the large pale cells similar to those in the spleen and lymph nodes, a fact that is difficult to explain According to Krylow<sup>33</sup> the suprarenal cortex regulates the lipid metabolism, and its inefficiency would cause the accumulation of local deposits of lipid in other organs No such deposit has hitherto been noted in the suprarenal medulla Possibly, this is because the other cells were filled with lipid and the accumulation still continued, resulting in a lipid infiltration of the reticulo-endothelium of the medulla But for this medullary change our case, histologically, seems to be a human counterpart of Anitschkow's experimental cholesterolsteatosis A more serious objection to this assumption of similarity is in the fact that both microchemically and quantitatively cholesterol was not the only lipid present, in fact, it was relatively less abundant than a lecithin-like body

The relation of our case to Gaucher's disease is a very important consideration, inasmuch as it deviates in some respects from the cases that have been reported The absence of any knowledge of the underlying cause of the lesions in Gaucher's disease, the paucity of the cases that have been thoroughly described, and the lack of unanimity of opinion among the different authors regarding the nature and origin of the large pale cells, some holding that they are endothelial cells (Bovaird,<sup>34</sup> Brill<sup>35</sup>), others that they are changed reticular or both reticular and endothelial cells (Risell,<sup>7</sup> Schlagenhauser<sup>36</sup>) and still others maintaining that they are derived from embryonic lymphoid cells (Mandelbaum,<sup>37</sup> Sapegno<sup>13</sup>) makes it difficult if not impossible to delineate what is the typical histologic picture of Gaucher's disease The differences of opinion are probably due to variation in the reaction of the cells to the underlying processes, resulting in the predominance of different cells in the individual cases Our case is the first one noted

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33 Krylow, D D Experimentelle Studien über Nebennierenrinde, Beitr z path Anat u z allg Path, 1914, lviii, 434, 474

34 Bovaird, D Primary Splenomegaly, Am Jour Med Sc, 1900, cxx

35 Brill, N E Mandelbaum, F S, and Libman, E Primary Splenomegaly, Gaucher Type, Am Jour Med Sc, 1905, cxxix, 491

36 Schlagenhauser, F Ueber mist familiar vorkommende, histologisch charakteristische Splenomegalien (Typus Gaucher (Eine Systemerkrankung des lymphatisch-hämatopoetischen Apparates), Virchows Arch f path Anat, 1907, clxxxvii, 125

37 Mandelbaum, F S The Pathology of Primary Splenomegaly, Jour Exper Med, 1912, xvi, 797

in an infant, and the more diffuse character of its lesions may well be the manifestation in an infant of the same process underlying Gaucher's disease. In this case the medulla of the suprarenal glands and the adventitia of some of the vessels showed the same accumulation of lipoid cells. The theory that Gaucher's disease involves only the hematopoietic organs is not entirely substantiated by the cases reported. In Risel's case a cluster of the large pale cells was noticed in the thyroid. Moreover, in most of the cases large numbers of the cells were described in Glisson's capsule of the liver as well as in the sinusoids, a fact that is opposed to the strictly hematopoietic nature of the disease. The only part of the liver that enters into blood formation during fetal life is the sinusoids. The explanation that the large lipoid cells are transported to the liver from the spleen by the blood stream is untenable, inasmuch as no such cells have ever been seen in the blood stream or in the portal vessels. It is much more probable that Gaucher's disease represents a "Systemerkrankung" not of the hematopoietic organs as such but of the reticulo-endothelial cells of the body, and most strikingly manifested in the hematopoietic organs, because of the prominence of the reticulo-endothelial cells in them. This conception would explain our case much more satisfactorily and also the cases of Gaucher's disease reported by the German authors. The streaking of the cytoplasm of the large pale cells, which was noted by Marchand<sup>6</sup> and Mandelbaum<sup>12</sup> was considered a characteristic of the cells in Gaucher's disease, but it has not been noted in the reports of most of the cases and is not peculiar to Gaucher's disease, inasmuch as Pick has shown that it occurs in the lipoid cells in old chronic granulation tissue of cases of chronic salpingitis,<sup>1</sup> and that it is due to the shrinkage of the cytoplasm following the solution of clusters of needle-like lipoid crystals. Consequently, this streaking indicates the presence of a cholesterol compound, but it is of minor anatomic importance and should play little part in the interpretation of the process as a whole, and its absence in our case does not mean that our case is not one of Gaucher's disease. The character of the large pale cells of our case and of the lipoid within them is identical with that of the cases of "grosszellige Hyperplasie" described by Schultze and Lutz and, based on the statements of these authors that the cells in their cases were identical with the cases of Gaucher's disease reported by Risel, Schlagenhauser and DeJong and Heukelom, and on the involvement of essentially the same tissues, we feel that we are fully justified in classing our case as an example of Gaucher's disease rather than reporting it as a unique and hitherto undescribed pathologic process.

The peculiar accumulations of lipoid cells, in Gaucher's disease, in cases of lipoidemia and in various subcutaneous tissues represent vary-

ing degrees of involvement of the same general system, that is, the reticulo-endothelial system (including the stellate cells of the liver) which controls the normal disposition of the lipoids of the body<sup>14</sup> Such accumulations are designated xanthelasmic diseases, and indicate a disturbance of lipid metabolism. The latter may be so seriously involved that the cells which normally dispose of the lipoids are unable to do so, resulting in a lipid infiltration of other cells, such as the parenchyma of the liver, a condition designated as myelinosis (Chalatow<sup>24</sup>). The causes underlying this disturbance of the metabolism are obscure, but Anitschkow's<sup>38</sup> work in producing local accumulations in subcutaneous tissue by inducing a general lipoidemia, from cholesterol feeding in rabbits and a local injury to the subcutaneous tissue, is very suggestive. It may well be that in these accumulations in man there is a predisposing susceptibility of the reticulo-endothelial system due to a disturbance in the lipid metabolism which may be manifested by a lipoidemia, and it only requires some toxic, or other injury of a part or of all of the system, to lead to a local or a general more diffused accumulation of lipid substances in this system. The factors that underlie the disturbances in lipid metabolism and the accumulation of lipid cells are unknown, but undoubtedly vary in the different cases, being more deep-seated and inherent in the body economy in the more diffused and extensive cases, such as in our case. In accordance with this conception, in Schultze's case of lipoidemia, accumulation of the lipid cells in the spleen represents a local involvement of the reticulo-endothelial system, the average case of Gaucher's disease, a more diffuse involvement of the same system, while our case of this disease represents an even more serious involvement, the accumulation of the cells occurring in the reticulo-endothelium of the suprarenal medulla and of the intestinal tract as well as in other tissue cells. The lipid substance is not necessarily the same in each case, for undoubtedly various combinations of lipoids occur with one predominating in one case, and another in other instances. While our case resembles in some respects Anitschkow's experimental cholesterolsteatosis, it is not an example of "Cholesterinester-Verfettung," inasmuch as both our microchemical and quantitative studies show that a lecithin-like body is the chief lipid present with also a prominent cholesterol body.

#### CONCLUSIONS

1 In Gaucher's disease the liver and the spleen show not only a marked increase in the lipid content, but also a serious alteration in normal relations of the lipids to each other. The fixed fats are greatly

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<sup>38</sup> Anitschkow. Ueber experimentelle erzeugte Ablagerungen von Cholesterinester und Anhäufungen von Xanthomzellen in subcutanen Bindegewebe des Kaninchens, München med. Wchnschr., 1913, No. 46.

reduced, while the lipoids, such as lecithin and cholesterol, are greatly increased. In our case a lecithin-like body predominated, but a cholesterol compound may prevail in other cases.

2 In Gaucher's disease, lipid substances accumulate in the form of small droplets within the cytoplasm of the tissue cells, resulting in the formation and accumulation of the distinctive large pale cells so characteristic, histologically, of this disease.

3 Gaucher's disease is due to a disturbance of lipid and fat metabolism, resulting in the accumulation of lipid substances in the cytoplasm of the large pale cells that are mostly transformed reticulo-endothelial cells of the spleen, lymph nodes and bone marrow and the stellate cells of the liver. These cells have the physiologic property of disposing of the fats and lipoids, and comprise the "endothelial Stoffwechselapparat." It is thus a system disease, but involves the hematopoietic organs only secondarily in that they are very rich in the reticulo-endothelial cells.

4 Those organs that contain the reticulo-endothelial cells in large abundance (spleen, lymph glands, bone marrow, liver, stellate cells of Kupfer, etc.) show the most changes, but specific parenchymal cells may absorb some of the lipid in a very advanced case.

5 Gaucher's disease belongs to the group of xanthelasmic conditions which are characterized by a more or less diffuse accumulation of lipoids in reticulo-endothelial or in fibroblastic cells in one or more organs. It represents a more diffuse and widespread involvement of the "Endothelial Stoffwechselapparat" than those cases of "groszellige Hyperplasie der Milz" in diabetic lipoidemia, with an underlying cause that is more deepseated and inherent in the body economy.

We wish to express our thanks to Dr J H Mason Knox, Jr, of Baltimore, for his courtesy in allowing us to use his material, to Dr Paul J Hanzlik for many valuable suggestions for our chemical study, especially in the evolution of our method for extracting the fats and lipoids, and to Prof Howard T Karsner for many suggestions and encouragement in carrying out our studies.

# THE CONTROL OF EXPERIMENTAL CRETINISM \*

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The work reported in this paper was undertaken at the suggestion of A J Carlson, primarily for establishing a biological test for the active principle of the thyroid gland in the blood

A few years ago Hunt,<sup>1</sup> by means of the acetone test, thought that he had a reliable test for the active principle of the thyroid in the blood. Later investigators (Carlson and Woelfel,<sup>2</sup> Lusk<sup>3</sup>) failed to detect any active principle of the thyroid in the blood of the dog, and in rabbits and guinea-pigs in experimental hyperthyroidism by means of this test. Hunt studied the blood of clinical cases of exophthalmic goiter and obtained a positive test in two out of three cases. On the other hand, Carlson and Woelfel could not get a positive reaction in a case studied by them. Carlson also tested his own blood after having taken thyroid until toxic symptoms arose, with negative results. The presence of iodine in the blood in "hyperthyroidism" has recently been shown by Jones and Tatum.<sup>4</sup> They found that intravenous injections of blood serum from hyperthyroid-fed rabbits increased the iodine content of the thyroid glands of the rabbits which were injected.

Another method of attack relates to the changes of excitability of the depressor nerve. Von Cyon and Oswald<sup>5</sup> found that injection of thyroid extract increases the irritability of the depressor nerve. Asher and Flack reported some interesting results on the excitability of the depressor nerve before and after stimulation of the thyroid nerves, and the effects of small intravenous injections of epinephrin before

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† From the Hull Physiological Laboratories of the University of Chicago

1 Hunt, Reid (a) Influence of Thyroid Feeding and of Various Foods upon Poisoning by Acetonitril, *Proc Soc Exper Biol*, N Y, 1905, *Jour Am Med Assn*, 1907, xlix, 1323, (b) The Probable Demonstration of Thyroid Secretion in the Blood in Exophthalmic Goiter, *Jour Am Med Assn*, 1907 xlix, 240

2 Carlson, A J, and Woelfel, A. On the Internal Secretion of the Thyroid, *Am Jour Physiol*, 1910, xxvi, 32

3 Lusk, H O. Further Studies of the Acetonitril Test for Thyroid Substance in the Blood, *Am Jour Physiol*, 1912, xxx, 63

4 Jones, A P, and Tatum, A L. On the Demonstration of the Variations in the Thyroid Colloid in Conditions of Hyperthyroidism and Hypothyroidism, *THE ARCHIVES INT MED*, 1913, xii, 225

5 von Cyon, E, and Oswald, A. Ueber die physiologischen Wirkungen einiger aus der Schilddrüse gewonnener Producte, *Pflüger's Arch f d ges Physiol*, 1901, lxxxiii, 199

and after such stimulation. The excitability of the depressor nerves is increased during or immediately following the stimulation of the thyroid nerves. According to Asher and Flack,<sup>6</sup> the animals are also sensitized to epinephrin through stimulation of the thyroid nerves. They ascribe these results to the action of increased quantity of thyroid secretion poured into the blood on stimulation of the thyroid nerves. After extirpation of the thyroid gland, stimulation of the thyroid nerves failed to produce increased excitability of the depressor nerve. According to their report, intravenous injection of thyroid extract acts similarly to stimulation of the thyroid nerves. Ossakin<sup>7</sup> (1914) working in Asher's laboratory repeated and apparently confirmed Asher and Flack's work.

The experiments were carried out on cretin rabbits produced by complete thyroidectomy. Five lines of investigation were undertaken:

- 1 The transfusion of normal blood serum
- 2 The transfusion of "hyperthyroid" blood serum
- 3 The feeding of Standard U S P thyroid products
- 4 The feeding of Koch's thyroid metaprotein
- 5 The feeding of Kendall's Extract B

#### I PRODUCTION OF CRETINS

The litters of rabbits were all raised from healthy albino stock of approximately uniform size. They were all kept in cages with their mother until 6 weeks of age, after which they were separated and the mother was again mated.

The animals were fed with oats, carrots, alfalfa hay and water daily. It is essential that the diet of the different litters be as uniform as possible, because of the great variation of growth curves with various foods. In this way the growth curves of various litters were made practically uniform.

Thyroidectomy was performed on the young rabbits at the age of 2 to 3 weeks, when their average weight was about 175 gm. One or two members of each litter were kept as controls. In the removal of the thyroids, the method of Hofmeister was followed, with usual aseptic procedures. Through a median incision of about 2 cm over the prominence of the larynx, the subcutaneous tissue and muscles were separated, bringing the thyroid cartilage into view. The thyroid glands lying on both sides of the trachea are, in rabbits, always connected at the lower pole by an isthmus, more or less flat and membranous. The gland is usually so closely adherent to the thyroid cartilage,

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6 von Asher, L., and Flack, M. Die innere Sekretion der Schilddrüse und die Bildung des inneren Sekretes unter dem Einfluss von Nervenreizung, *Ztschr f Biol*, 1911, 1v, 83.

7 Ossakin, N. Zur Frage des Innervation des Glandula Thyroidea, *Ztschr f Biol*, 1914, 1viii, 444.

especially at its posterior end, that it can be separated only with difficulty. With a fine pointed probe, the lower pole is carefully separated from the recurrent laryngeal nerve and the surrounding pericapsular tissue. It is essential that the recurrent laryngeal nerve should not be injured because of the fatal dyspnea following such an injury. Care was also taken to leave the external parathyroids intact. One or more may usually be seen in the pericapsular tissue. The arteries were either ligated before division or, if small, they were clamped and crushed with forceps before division. The thyroid tissue was carefully dissected away from the thyroid cartilage and this lobe, together with the connecting isthmus, was reflected over the remaining lobe. This lobe was separated in a similar way.

Great care has to be taken to remove all of the thyroid tissue, because it is surprising how fast small remnants of tissue will hypertrophy. Such remnants, if present, on postmortem examination were usually found on the posterior end, closely adherent to the thyroid cartilage. These nodules always showed marked evidence of hypertrophy. However, these remnants were never more than one-tenth of the size of one of the lobes. Out of over 140 operations I have produced typical symptoms of cretinism in eighty-six cases. There is also some variation in the different litters in the location of the gland with respect to the thyroid cartilage. In some litters, on account of the difficulty of removal it was impossible to get cretins in more than 25 per cent of cases. On the other hand, the perfect ease with which the thyroid gland could be removed in other cases was shown by the development of symptoms of cretinism in 90 per cent after operation. Experimental cretinism in rabbits has been studied by Moussu,<sup>8</sup> Hofmeister,<sup>9</sup> Haushalter and Jeandelize,<sup>10</sup> Leonhardt,<sup>11</sup> Blumreich and Jacoby,<sup>12</sup> and Tatum.<sup>13</sup>

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8 Moussu. Effets de la thyroïdectomie chez nos animaux domestiques, *Compt rend Soc de biol*, 1892, xlv, 271.

9 Hofmeister, F. (a) Experimentelle Untersuchungen über die Folgen des Schilddrüsen Verlustes, *Beitr z klin Chir*, 1893-94, xi, 441, (b) Zur Frage nach den Folgezuständen bei Schilddrüsenexstirpation, *Deutsch med Wchnschr*, 1896, xxii, 354, (c) Über Störungen des Knochenwachstums bei Kretinismus, *Fortschr der Röntgenstr*, 1897-1898, 1.

10 Haushalter, P, and Jeandelize, P. Retard de développement et état cretinoïde à la suite de la thyroïdectomie chez un agneau et chez un lapereau, *Compt rend Soc de biol*, 1902, liv, 597.

11 Leonhardt, M. Experimentelle Untersuchungen über die Bedeutungen der Schilddrüse für des Wachstum im Organismus, *Virchow's Arch f path Anat*, 1897, cxlix, 341.

12 Blumreich, S, and Jacoby, M. Experimentale Untersuchung über die Bedeutung der Schilddrüse und ihrer Nebendrüsens für den Organismus, *Pflüger's Archiv f d ges Physiol*, 1896, lxiv, 1.

13 Tatum, A. L. Morphological Studies in Experimental Cretinism, *Jour Exper Med*, 1913, xvii, 636.

In the present series the onset and development of the cretin symptoms were always similar. About two weeks after the operation the hair becomes noticeably drier and does not lie smooth and flat on the skin as normally. It stands up and can be pulled out very easily. At the same time there is a gradual retardation of growth. This is noticeable as early as the third week after the operation. This retardation of growth is greatest from the eighth to the twelfth week, as shown in Figure 1. By the tenth week, the average weight of the cretins is 750 gm, while the normal controls weigh approximately 1,400 gm. From this time the growth curve of the cretins deviates even more rapidly from that of the normal, but the growing period is longer in the case of the cretins. This was true in all cases under observation.

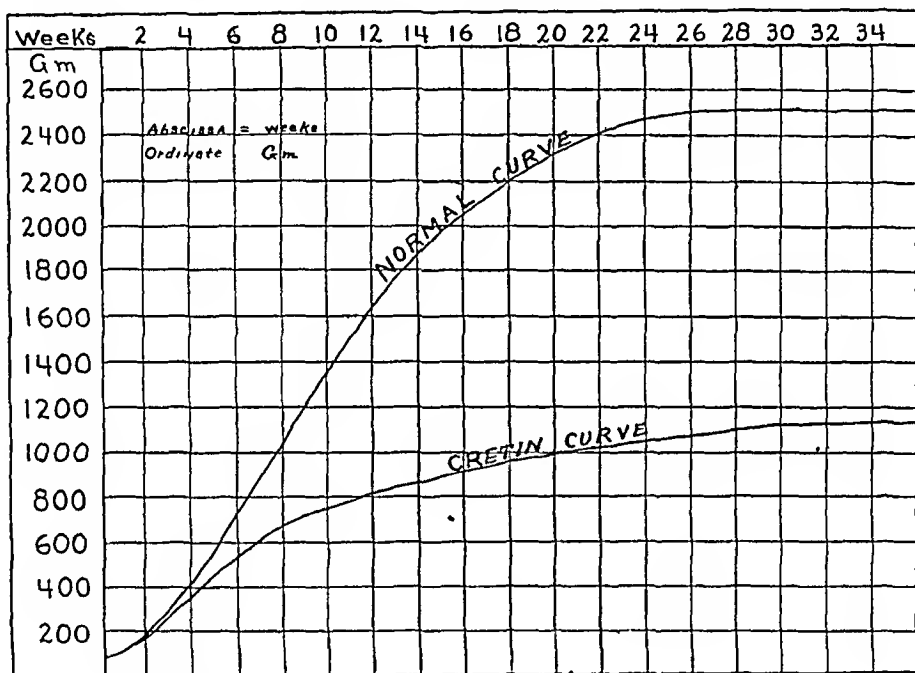


Fig 1—The growth curves of four normal control and three cretin rabbits

Figure 2 shows two typical cretins with normal control at the age of 12 weeks. The weight of the normal rabbit is 1,630 gm, while the weights of the cretins are 760 and 840 gm, respectively. The posture of the cretin is typical. The limbs are short and the muscles are too weak for support. The bones show a pseudorickety condition which Hofmeister<sup>9</sup> calls "chondrodystrophia thyreopriva." The hair becomes coarse and can be pulled out in bunches. The skin becomes dry, thick and scaly, gradually turning into a typical eczema covered with crusty scales. This is always most marked about the head, ears, shoulders and legs. The proportionate growth of the abdomen over that of the rest of the body gradually increases and the cretin acquires the descriptive "pot belly" type of abdomen. They are slow, awkward and move about very reluctantly. If not disturbed, they may remain for hours



in the same place Haushalter and Jeandelize<sup>10</sup> speak of a swollen, myxomatous condition of the skin which developed gradually in all of their cretins. There was no typical myxedema noticed in any of my cretins. It is evident that myxedema so characteristic of post-operative thyreopriva in man, is not an accompanying symptom of cretinism in rabbits. The chronic, progressive fatal cachexia described by Hofmeister, was not apparent in my cretins. I have kept sixteen cretins alive for over a year without any evidence of cachexia as described by Hofmeister. Of course, there was a marked muscular weakness, especially noticeable in the limbs, but the animals always appeared to be in a fairly well nourished condition.



Fig. 2—Normal control rabbit and two cretins from same litter. Age 12 weeks. Weight of normal, 1,630 gm., cretins, 840 and 760 gm.

## II BLOOD TRANSFUSION

(a) *Normal Blood Serum*—The blood serum used for transfusion was taken from rabbits from the same stock as those used for experiments. Sixteen normal, healthy grown rabbits were kept for bleeding purposes. These were bled alternately, and never oftener than once every three weeks, for the purpose of keeping the animals in the best possible condition and for giving the thyroid gland a chance to replenish its secretion, assuming that it has an internal secretion. The greatest possible aseptic precautions were taken in all these experiments. The animal was bled 25 c.c. from the ear, the blood defibrinated,

filtered at once, rapidly centrifuged and the serum injected intravenously into the cretin rabbits. Four cretins averaging 350 gm were used for transfusion. Injections were made into the ear veins, under the usual aseptic precautions, with a fine needle. The amount injected in the four cases varied from the beginning of the experiment, the smallest being 2 c c and the largest 5 c c. These transfusions were made four times weekly. There was no evidence of any toxicity, so these doses were gradually increased. Toward the end of the experiment, the amount injected in the four cases ranged from 6 c c to 10 c c. Figure 3 represents the average growth of the controls and of the cretin rabbits which have been transfused. The normal cretin curve is identical with the lower curve. Suffice it to say, that these curves

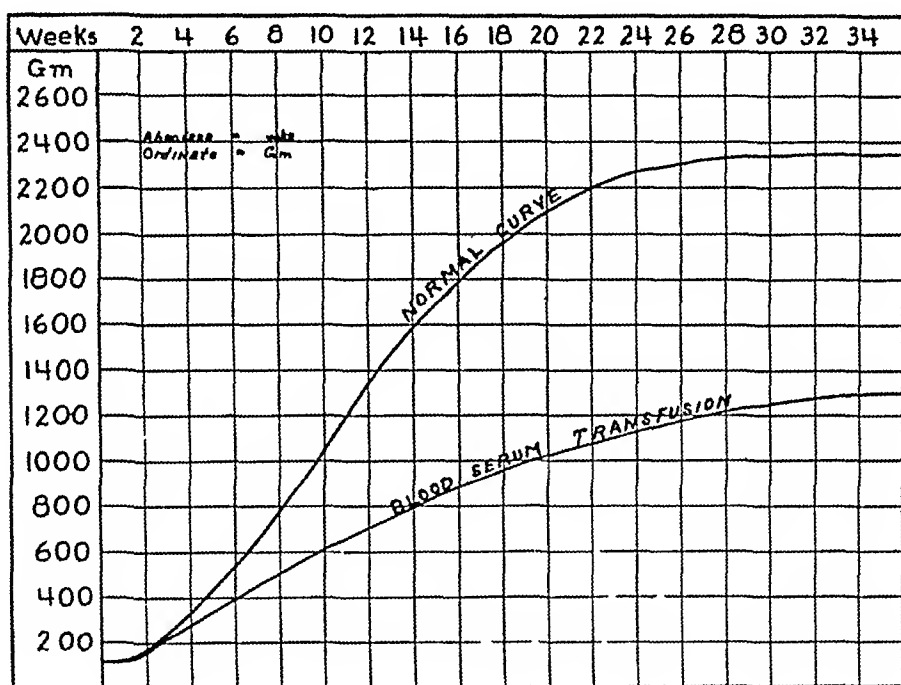


Fig 3—The growth curves of three normal controls and four cretin rabbits which had been transfused with normal blood serum

differ in no respect from those of Figure 1, except that the maximum growth of control, normal cretin and transfused cretin are somewhat less.

Figure 4 shows a control rabbit with two cretins at the age of 16 weeks after transfusion of the cretin for two and one-half months. The weight of the control was 1,850 gm, and that of the cretins 890 and 950 gm, respectively. There is no evidence of any improvement due to the transfusion. They are essentially cretins differing in no respect from the normal cretins shown on the other pictures.

(b) "*Hyperthyroid*" Blood Serum—Fifteen normal, healthy, grown rabbits were kept in separate cages as in the preceding experiment. These were fed increasing doses of Standard U S P thyroid

four times per week, until symptoms of toxicity resulted. This overdose of thyroid, or "hyperthyroidism," was kept up throughout the experiment. The average toxic dose for these rabbits was 0.65 gm. The animals were bled alternately as in the preceding experiments. The procedures, as bleeding, centrifuging and transfusions were similar. The same general precautions were taken to have the transfusion



Fig 4—Normal control and two cretin rabbits which were transfused with normal blood serum. Age, 16 weeks. Weight of normal, 1,850 gm, cretins, 890 and 950 gm.

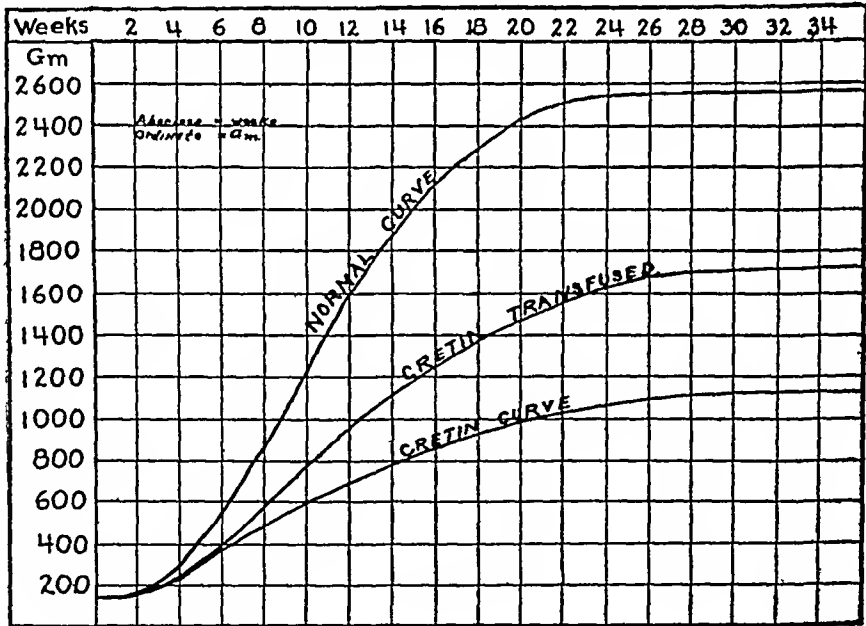


Fig 5—The growth curves of four normal controls, two cretins, and six cretins which had been transfused with "hyperthyroid" blood serum.

done under as nearly sterile conditions as possible. Six cretin rabbits from four litters, containing eight cretins and four normal controls, were used for transfusion. Injections were begun on the fourth week with amounts varying from 3 to 5 cc. These transfusions were made four times a week. Cretin rabbits weighing 350 gm will not tolerate

more than 5 c c because of the apparent toxicity of this serum. These doses were gradually increased as in the preceding experiments. By the twentieth week, the amount injected varied from 8 to 12 c c in the different rabbits.

The growth curves are shown in Figure 5. The upper curve represents the growth of normal, the lower, the normal cretin, and the middle, the growth curve of the cretin rabbits which had been transfused with the "hyperthyroid" blood serum. The upper and lower curves are similar to the curves of preceding figures. The middle curve is typical of the effects of transfusion of the "hyperthyroid" blood serum. During the first two weeks, there is no change from the normal cretin curve, after which there is a gradual increase. This increase, however, is not so marked as in the cretins which had been fed thyroid. The average maximum growth attained in the six cretins which were injected, was 1,750 gm. The average weight of the normal



Fig 6—Normal control and two cretin rabbits from same litter. Age, 28 weeks. Transfused with "hyperthyroid" blood serum. Weight of control, 2,350 gm, cretins, 1,650 and 1,720 gm.

was 2,550 gm and that of cretins, not transfused, 1,125 gm. This gives an average increase in weight of transfused rabbit of 600 gm over that of normal cretins.

Figure 6 shows two transfused cretins and one control at the age of 28 weeks (7 months). The weight of the control is 2,550 gm and of transfused, 1,650 and 1,720 gm, respectively. The hair is abundant, smooth and lays flat. The skin shows no signs of any scaly or eczematous condition. The weakness of muscles, bones and joints has disappeared. The animals appear as alert and active as the normal rabbits.

### III THYROID FEEDING

The clinical literature on the beneficial effects of thyroid feeding on cretinism seems conclusive. In man, however, it is frequently difficult to decide whether we are dealing with cases of pure cretinism due to deficiency of thyroid activity, or with other diseases.

Kutschera,<sup>14</sup> who had more than one thousand cases of cretins under observation, claims that it is often next to impossible to differentiate cretinism from certain forms of rachitis. Thyroid medication on these patients was carried on by Kutschera over a period of two years, with complete cure in 42.8 per cent of the cases, decided improvement in 48.6 per cent, and in 8.6 per cent there was no evidence of any improvement. The hair became normal, myxedema disappeared and bone deformities decreased. Kutschera plotted many growth curves, showing that in 377 cases the increase of growth was above that of the normal. Many clinicians and investigators, however, could not bring the growth of cretins up to that of the normal individual. Kutschera says that the increase of growth can be taken as the best criterion of the value of thyroid therapy.

Pick and Pineles,<sup>15</sup> in 1910, reported their results on the activity of various laboratory preparations in experimental cretinism in young goats. With the desiccated thyroid there was a rapid improvement. A thyroidin preparation was negative in activity. On the other hand, earlier investigators (Baumann,<sup>16</sup> Ewald,<sup>17</sup> Lichtenstern, Magnus Levy<sup>18</sup>) claim that thyroidin is just as active in removing the symptoms of thyroid deficiency as the desiccated thyroid. The results of the earlier investigators, however, are of little value because their work was mostly confined to dogs which died early of parathyroid tetany, due to removal of the parathyroids with the thyroids. According to Pick and Pineles, the symptoms of cretinism can be controlled by feeding thyreoglobulin. Oswald<sup>19</sup> and Magnus Levy<sup>18</sup> also found that thyreoglobulin is active. Moreover, Pick and Pineles<sup>15</sup> found that pepsin and trypsin split products are still effective when digestion is not allowed to go on for a long time. Long continued digestion will entirely destroy the thyroid activity. If Hunt's acetonitril

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14 Kutschera, V. (a) *Das Groszenwachstum bei Schilddrusenbehandlung des endemischen Kretinismus*, *Wein klin Wchnschr*, 1909, xxii, 771, (b) *Der endemische Kretinismus, seine Ursachen, und seine Behandlung*, Wien, Alfred Holder, 1911.

15 Pick, E. P., and Pineles, F. *Untersuchungen uber die Physiologisch Wirksame Substanz der Schilddruse*, *Ztschr f exper Path u Therap*, 1909, vii, 518.

16 Baumann, E. *Ueber die Wirksamkeit des Thyroidins*, *Munchen med Wchnschr*, 1896, xliii, 476.

17 Ewald, J. R., and Rockwell. *Exstirpation der Thyreoidea an Tauben*, *Pfluger's Arch f d ges Physiol*, 1890, xlvii, 160.

18 Magnus-Levy. (a) *Uber Myxodem*, *Ztschr f klin Med*, 1904, lii, 201, (b) *Organtherapie und innere Sekretion*, *Mod artztl Bibl*, Berlin, 1906, (c) *Die Therapie d Gegenw*, 1907.

19 Oswald, A. (a) *Die Schilddruse und ihr Wirksames Principel*, *Biochem Centralbl*, 1903, i, 249, (b) *Die Eiweiskorper der Schilddruse*, *Ztschr f physiol Chem*, 1899, xxvii, 14.

test is to be taken as a reliable method of judging the activity of a given thyroid preparation, then the above results agree with those of Koch,<sup>20</sup> who determined the activity of different split products of thyroid by means of the acetonitril test. He found that the thyroglobulins and metaprotein fractions are more active than the original product. The other products of thyroid hydrolysis, iodothyrim, primary and secondary albumose, show a marked decrease of activity. Lower split products are entirely inactive.

Recently Kendall<sup>21</sup> reported some interesting results on certain split products of the thyroid gland which he calls "Extract A" and "Extract B." Extract A affects the nitrogen metabolism, body weight and temperature. It causes marked tachycardia, nervousness and tremors. Extract B shows no toxicity. The skin and hair become entirely normal in human cretins. The weakness of muscles, bones and joints soon disappear. Schaefer<sup>22</sup> found that the addition of small amounts of thyroid tissue to the normal diet of white rats causes a great increase of food consumption with acceleration of the growth curve. Recently, Gudernatsch<sup>23</sup> fed fresh thyroid tissue to young tadpoles and found that this tissue has the power to excite differentiation, but it lacks the power to produce growth. On the other hand, he claims that thymus and spleen cause growth without differentiation. It is evident, however, that since the thyroid tissue is rather toxic, as Gudernatsch has shown in a later paper, this retardation of growth may be due to overfeeding with thyroid tissue.

#### A STANDARD U S P PRODUCTS<sup>24</sup>

The cretins were produced experimentally according to the method described above. Eight cretins from four litters were fed with the desiccated thyroid. As soon as the symptoms of cretinism appeared, which was usually at the beginning of the third or fourth week, thyroid feeding was started. The thyroid was weighed out in small-size

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20 Koch, F. C. On the Nature of the Iodin-Containing Complex in Thyroglobulin, *Jour Biol Chem*, 1913, xiv, 101.

21 Kendall, E. C. (a) Specific Physiological Activity of Certain Constituents of the Thyroid Gland, *Proc Soc Exper Biol and Med*, 1912, x, (b) A Method for the Decomposition of Proteins of the Thyroid, with a Description of Certain Constituents, *Jour Biol Chem*, 1915, xx, 501.

22 Schaefer, E. A. The Effects upon Growth and Metabolism of the Addition of Small Amounts of Ovarian Tissue, Pituitary and Thyroid to the Normal Dietary of White Rats, *Quart Jour Exper Physiol*, 1912, v, 3.

23 Gudernatsch, J. F. Feeding Experiments on Tadpoles, *Am Jour Physiol* 1914, xxxvi, 370, *Am Jour Anat*, 1914, xv, 431.

24 Armour's Standard U S P Desiccated Sheep Thyroid was used. This preparation is fairly uniform in activity and contains approximately 0.2 per cent iodine in organic combination.

gelatin capsules. Such capsules can be fed without much difficulty. The initial dose was 0.015 gm given daily. Cretin rabbits are very susceptible to thyroid feeding. Toxic symptoms develop with much smaller doses than with the normal rabbit of the same size. This is evidently due to the absence of the thyroid gland, which normally has been shown by Jones and Tatum<sup>1</sup> to take the organic iodine out of the blood very quickly. The animals were weighed twice a week and if there was any evidence of toxicity as shown by the growth curve, and other symptoms, then the dose was reduced. This dose was gradually increased. By the twentieth week the amount given was on the average 0.075 gm. Great care had to be taken to prevent toxicity because

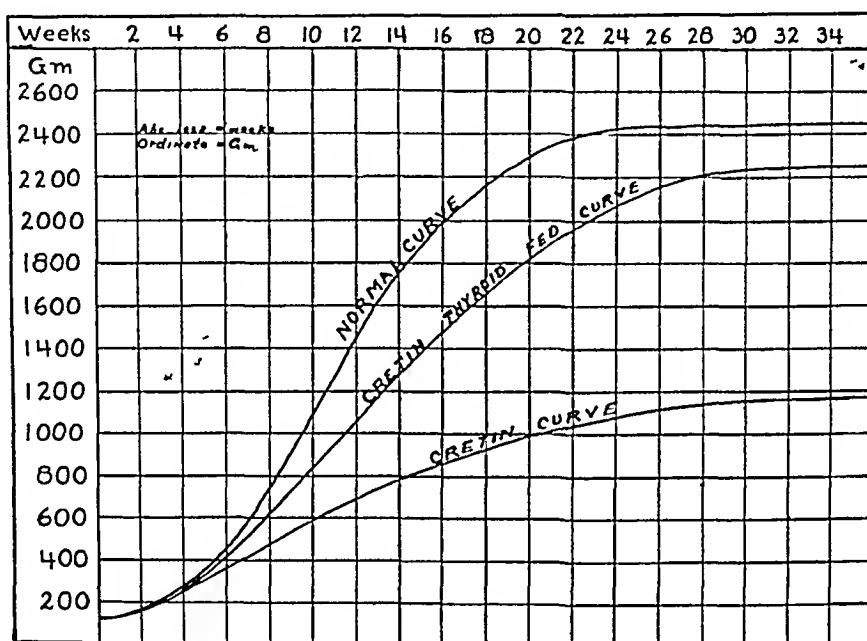


Fig 7—The growth curves of four normal controls, five cretins, and of eight cretins which were fed standard U S P thyroid preparations

usually the animal lost so much weight that it took several weeks merely to recover his original weight.

Figure 7 represents the average growth of seventeen rabbits. The upper curve represents the average growth of the four normal controls. In this connection it may be said that the variation in growth is negligible, making it unnecessary to plot separate curves. The growth gradually increases up to the twelfth week, after which there is a gradual decrease. This decrease is most marked from the twentieth to the twenty-fourth week. The average weight of four normal rabbits is 2,475 gm. The lower curve represents the average growth of the cretins of the four litters which had not been fed thyroid. The variation in weight in the four cretins was negligible. As can be seen in Figure 7, the growth curve increases up to the fifth week, after which

there is a gradual retardation of growth. This slight difference in weight from the normal from the second to the fifth week is evidently due to the operation. The maximum growth is reached at the thirtieth week ( $7\frac{1}{2}$  months). The maximum average weight of the cretins was 1,175 gm. The maximum growth in the normal rabbit is reached about six weeks before that of the cretin rabbits. This was evident in all cretins under observation.

The second curve represents the growth of the eight cretin rabbits that had been fed thyroid. The curve is identical with the normal cretins up to the fifth week, after which there is a gradual increase, but this increase does not approach the normal curve. The maximum growth is reached about the thirty-second week (8 months) when the



Fig 8—Normal control (right) and cretin from same litter fed standard thyroid preparation. Age, 20 weeks. Weight of control, 2,210 gm, of fed cretin, 1,860 gm.

weight is 2,250 gm. *Growth continues about eight weeks after the maximum growth of the normal rabbit has been reached.* In no case was it possible to reach the growth of normal rabbits, as some investigators claim to have done. This was probably due to the fact that feeding experiments are difficult to control because of the lessened resistance to the thyroid feeding.

The symptoms of cretinism gradually disappeared. The hair became smooth and attained the moist, oily appearance of the normal rabbit. The scaly condition of the skin about the ears and legs disappeared. The pot belly, so characteristic of cretins about the eighth week, gradually disappeared. The animals became more active and



the weakness of the muscles, bones and joints was not noticeable after six weeks' feeding. Deformities of the bones never appeared in any of the thyroid-fed rabbits. This is evident from a comparison of the two rabbits in Figure 8. It represents the typical results of thyroid feeding. The age of the animals in the litter is 20 weeks. The normal rabbit on the right weighs 2,210 grams, while the left thyroid-fed rabbit weighs 1,860 gm. A comparison with the cretin rabbits which were not fed thyroid will show the absence of symptoms in the thyroid-fed rabbit. In all the cretins and thyroid-fed rabbits under consideration, no thyroid tissue was evident at necropsy.



Fig 9—Two thyroid-fed cretins. Feeding discontinued for five months.

When the thyroid feeding in the cretins is discontinued for some time, certain symptoms of thyroid deficiency soon become evident. This is evident from Figure 9. Thyroid feeding had been discontinued in the two rabbits for five months. They appeared perfectly normal when the thyroid feeding was stopped. The hair soon became dry, coarse, and could easily be pulled out in bunches. The skin became dry, scaly and gradually became eczematous. This was most evident on forehead, ears, legs and abdomen. The weakness of bones, muscles and joints also reappeared. The animals once more acquired the typical symptoms of cretinism, and except for their size, which was induced by thyroid feeding, could not be differential from cretins which served as controls.

B FEEDING OF THYROID METAPROTEIN<sup>25</sup>

The cretins were produced as in the previous experiments. The results are based on seven rabbits in two litters having two controls and five cretins. It was found that this preparation was considerably more toxic than the standard U S P thyroid, and it was necessary to reduce the dose to 0.005 gm, given daily to prevent toxicity. This dose was gradually increased to 0.05 gm. The cretins continued to grow till the end of the thirty-second week (eight months), when they attained the maximum weight of 1,950 gm. This period is a somewhat longer growth period than in the normal control.

Figure 10 represents the growth curves of the normal, normal cretins, and cretins which were fed the metaprotein compound. The

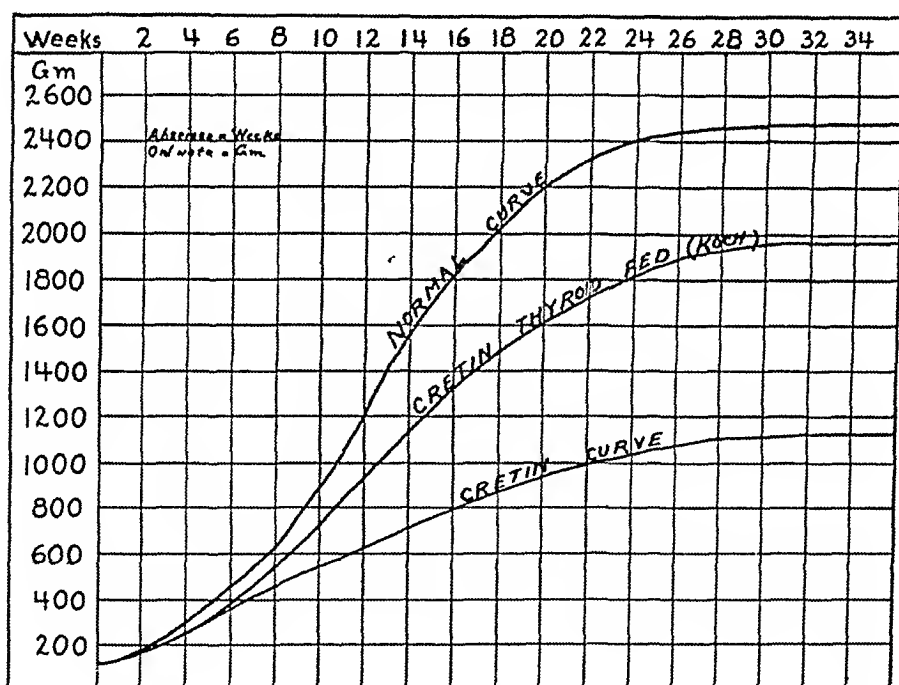


Fig 10—The growth curves of two normal controls, two cretins, and of three cretins which were fed Koch's metaprotein thyroid product

normal and cretin growth curves are very similar to those of Figure 7. The middle curve represents the average growth of the three cretins fed with the thyroid metaprotein. There is a gradual increase of the growth as early as a week following the use of the preparation. After the sixteenth week there is a gradual decrease of the growth. Comparing Figures 7 and 10, it is seen that the increase of growth is not as marked with feeding the metaprotein compound as with the standard

<sup>25</sup> This thyroid split product was prepared by Dr Koch in the biochemical laboratory. It is a metaprotein compound prepared from sheep thyroids and contains approximately 15 per cent of iodine in organic combination. As tested by the acetonitril test, Koch found it considerably more active than standard thyroid preparations.

U S P preparations This may be explained partly by the increased difficulty of regulating the dosage because of the greater toxicity of the metaprotein over that of the standard U S P product When referring to toxicity, I have reference to the symptoms of overfeeding or "hyperthyroidism," namely, diarrhea, tachycardia, tremor and nervousness

C KENDALL'S THYROID EXTRACT B<sup>26</sup>

The animals used for these experiments were taken from two litters having three normal controls and five cretins Three of these cretins were fed "Extract B" It was found that this preparation was non-toxic There was no improvement either in the growth curve or in

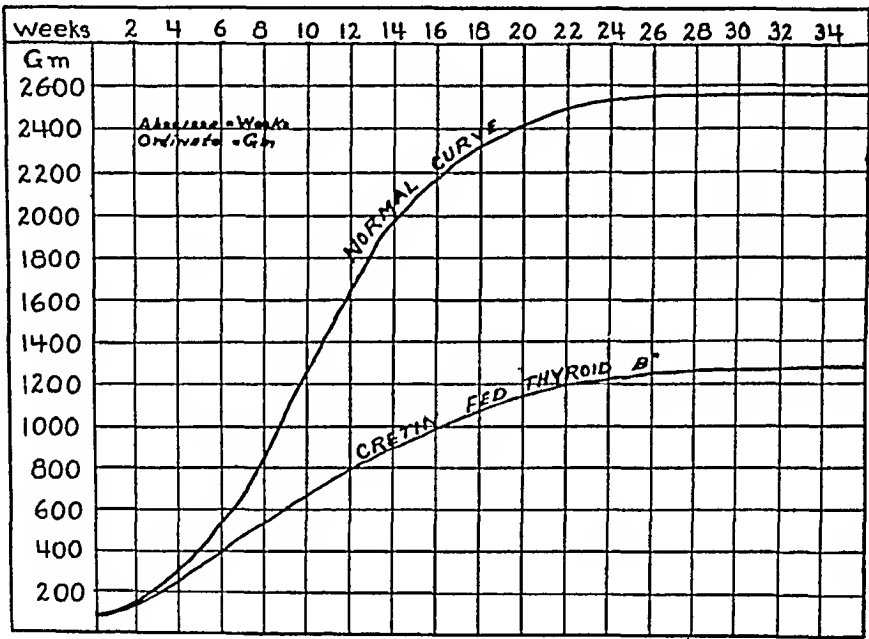


Fig 11—The growth curves of three normal controls and of five cretins, three of which were fed Kendall's Extract B

any of the other symptoms of cretinism Increasing doses were given up to 0.5 gm, with negative results

In Figure 11, we have the growth curves of normal control and cretin rabbits which have been fed Extract B This latter curve is identical with that of the normal cretin These curves are very similar to those of Figure 1 As far as growth is concerned, these results agree with those of Kendall As pointed out before, he claims its chief effect in man to be on the hair and skin The weakness of muscles, bones and joints, and the mental activity are greatly improved,

26 Both the chemistry and its physiologic properties are described in the recent paper by Kendall

according to Kendall. On the other hand, my results were entirely negative. This can be readily seen by comparing A and B of Figure 12. They represent two cretins and a normal control taken at the age of 7 and 20 weeks, respectively. A was taken at the age of 7 weeks, just before feeding was started. The weight of the control was 820 gm and that of the cretins, 480 and 360 gm, respectively. B represents the same litter after twelve weeks (three months) of feeding with the thyroid Extract B. The weight of the control was 2,375 gm and of the cretins 1,200 gm and 1,250 gm, respectively. The hair, skin and pot belly show no improvement. The weakness of muscles, bones and joints is especially marked.

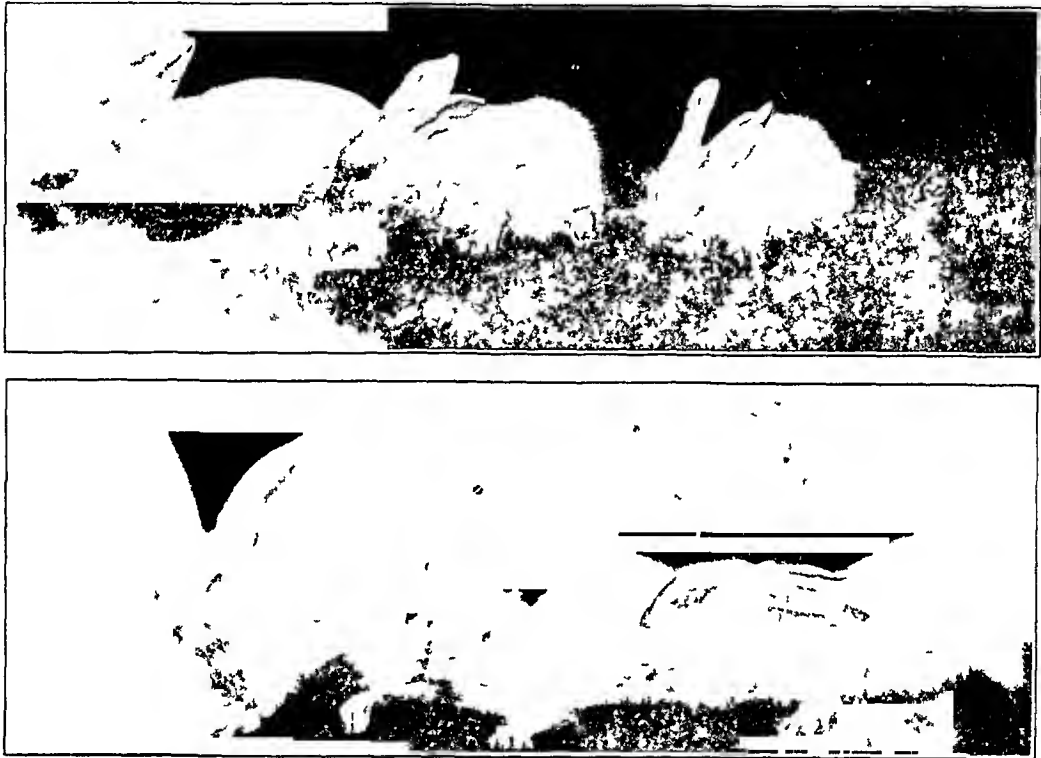


Fig 12—A (above) age 7 weeks. Normal control weighing 820 gm and two cretins weighing 360 and 480 gm, respectively. B (below) same litter as A after feeding Kendall's Extract B. Age, 20 weeks. Normal weighs 2,375 gm and cretins 1,200 and 1,250 gm, respectively.

#### IV COMMENTS ON THE RESULTS

The feeding experiments show that experimental cretinism can be very effectively controlled by the use of standard thyroid preparations. It is evident from the experiments, that a very small dose given daily is sufficient to supply the physiological needs. This amount ranges from 0.015 gm given daily at the beginning of the experiment, to 0.075 gm at the age of 20 weeks. Toxicity from thyroid feeding is more readily induced in cretins than in normal rabbits of the same age.

Since it is known that the thyroid gland has a great chemical affinity for iodine and iodine compounds, there would probably seldom be an excessive amount of the active principle of the thyroid in the blood of normal rabbits. This probably accounts for the greater toxicity in thyroidectomized rabbits.

Cleavage products prepared from desiccated or fresh thyroids are still active if this hydrolysis does not go too far. Koch's metaprotein compound containing 1.5 per cent iodine in organic combination is more active than standard U. S. P. desiccated thyroid containing about 0.2 per cent iodine. Doses one-third the weight of the standard product are sufficient for physiological needs. That the activity of thyroid preparations depends, within certain limits, on the amount of iodine in organic combination, has been shown repeatedly.

Kendall's Extract B, although containing 40 per cent of the total iodine, has no effect on the growth curve or on the other symptoms of cretinism, namely, that of hair, skin and weakness of muscles, bones, and joints. This preparation was found to be nontoxic to cretins and normal controls. Presumably, hydrolysis has gone too far, and the iodine is not in its normal organic combination.

Transfusion of normal blood serum has no effect on the growth and the other symptoms of cretinism. The animals remained identical with the cretins which were not transfused. No toxicity resulted from the injections. The negative results, however, do not disprove the theory of an active principle of the thyroid in normal blood. It was impossible to make more complete or more frequent transfusions. Furthermore, it is known that the equivalent of only a few milligrams of iodine in organic thyroid combination given daily is sufficient for normal physiological conditions. These results also agree with those of other investigators who have applied Hunt's acetonitril test to normal blood with negative results.

Transfusion of "hyperthyroid" blood serum increased growth considerably. The other symptoms, as that of the hair, skin, pot belly, weakness of muscles, bones and joints, also showed marked improvement. The increase in growth is, however, not as marked as with the feeding experiments. This growth curve never reached more than two-thirds that of the normal curve. The fact that we get marked improvement in cretins, however, is direct evidence of the presence of an active principle of the thyroid in the blood of "hyperthyroid"-fed rabbits. It must be granted, however, that these active principles of the thyroid probably represent the product absorbed from the gastrointestinal tract and not that of an internal secretion of the animal's own thyroid gland.

## V SUMMARY

1 Transfusion of normal blood serum into cretins has no effect on the condition of cretinism

2 Transfusion of "hyperthyroid" (thyroid-fed animal's) blood serum into cretins is effective in increasing the growth and in controlling the other symptoms of cretinism The improvement, however, is not as marked as with the thyroid feeding

3 Standard thyroid preparations (containing 0.2 per cent iodine in organic combination), when given in carefully controlled nontoxic doses, will increase the growth of cretin rabbits and prevent the development of, or counteract, the other symptoms of cretinism But thyroid feeding fails to carry an absolute cretin to full normal stature Discontinuing the thyroid feeding leads to a return of some of the cretin symptoms

4 The thyroid metaprotein of Koch is somewhat more active than standard thyroid preparations, but also more toxic

5 Kendall's thyroid Extract B has no effect on any of the symptoms of cretinism It is nontoxic, at least in ordinary doses

6 Cretins are more susceptible than the normal animals to the toxic action of thyroid (thyroid feeding)

7 Cretin rabbits, despite their retarded rate of growth, continue to grow for a considerably longer time (four to six weeks) than the controls of the same litter

I wish to express my great appreciation to Dr Carlson for valuable suggestions and criticisms, also to Drs Koch and Kendall who kindly gave me samples of their thyroid cleavage products for use in my experiments

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# AGGLUTINATION IN PERTUSSIS

ITS CHARACTERISTICS AND ITS COMPARATIVE VALUE IN CLINICAL DIAGNOSIS, AND IN DETERMINATION OF GENUS AND SPECIES<sup>\*</sup>

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## INTRODUCTION

The work herewith reported is part of a series of studies on pertussis begun by the Bureau of Laboratories of the New York City Health Department in 1914 under direction of Dr A W Williams<sup>1</sup>. The subject of agglutination was taken up chiefly because of the different reports given by various authors as to the value of agglutination and of complement fixation in the early clinical diagnosis of pertussis, and because of the comparatively few definite reports made on the value of former test

## CRITICAL STATEMENT OF PREVIOUS FACTS

All authors (at least those who give some details about their work) are agreed that agglutinins for *B pertussis* may be produced in most test animals but statements are vague as to the time and amounts of production and the condition under which they are produced

The general statement is usually made that after several inoculations made preferably into the peritoneal cavity, the serum of the animal showed agglutinins. The reports on the strength of the serum, if stated at all, is varied. Thus Bordet and Gengou<sup>2</sup> obtained in rabbits after four inoculations intraperitoneally a serum which the authors say was not as strong as that of the horse which was inoculated many more times subcutaneously and intravenously. Arnheim<sup>3</sup> obtained a serum in rabbits of 1 to 5,000 strength and in the horse 1 to 10,000, but he gave no details of methods and times of inoculation. Wollstein<sup>4</sup> by

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<sup>\*</sup> From the Research Laboratory, Health Department, New York City

1 Williams, Anna Wessels. The Etiology of Pertussis, Arch. Pediat., 1914, **xxxi**, No 8

2 Bordet, J, and Gengou. Note Complementary sur le microbe de la coqueluche, Ann d l'Inst Pasteur, 1907, **xxi** 720

3 Arnheim, Georg. Ueber den gegenwartigen stand der Keuchhustenfrage, Berl med Wchnschr 1908 **xl**-II, 1453

4 Wollstein Martha. The Bordet-Gengou Bacillus of Pertussis Jour Exper Med, 1909, **xi**, 41



intraperitoneal inoculations obtained a serum in the rabbit up to 1 to 800. Intravenous inoculations were not successful. No details of amounts or time of inoculation are given. Bacher and Menschikoff,<sup>5</sup> Shiga, Imai, Euguchi<sup>6</sup> found agglutination tests in pertussis of no value, as their bacillary emulsions were self-agglutinating.

Wollstein,<sup>4</sup> Frankel,<sup>7</sup> Seiffert,<sup>8</sup> Arnheim,<sup>3</sup> found agglutination tests of some value in clinical diagnosis of pertussis. Renaux<sup>9</sup> did not think it worth while to try.

Bordet<sup>10</sup> finds it of value only under certain conditions, namely, the organism must be freshly isolated from human sputum and grown on rich blood medium. The work of Bordet on agglutination will be dwelt on more in detail later.

#### ORIGINAL WORK

Our studies may be divided into the following:

1 The determination of the best conditions under which agglutinating serum may be obtained in test animals.

2 The comparative value of the test in demonstrating specificity of strains isolated by us from human beings suffering from whooping cough.

3 To add further evidence as to the comparative value of complement fixation and agglutination in the clinical diagnosis of pertussis.

1 *The Production of Agglutinins*—Rabbits, horses, goats and sheep were used by us in producing agglutinins. Rabbits and horses responded more readily than the goats and sheep, so most of the tests have been made with serums from the former animals. Practically all of the rabbits inoculated (over 95 per cent) which have remained in good health have produced abundant agglutinins for *B. pertussis*, though not all equally abundant.

*Antigens Used*—We have worked with twenty-seven strains of culturally and morphologically typical Bordet-Gengou bacilli (*B. pertussis*) with nine strains of *B. influenzae*, with four strains of *B. bronchisepticus*, and with four

5 Bacher, St., and Menschikoff, V. K. Ueber die aetiologische Bedeutung des Bordetschen Keuchhustenbacillus und den Versuch einer Spezifischen Therapie der Pertussis, Centralbl. f. Bact., 1911, 1 Abt. Orig., 141, No. 3, p. 218.

6 Shiga, X., Imai, N., and Euguchi, Ch. Eine Modifikation für Bordet Gengou's Nährboden für die Keuchhustenbacillen nebst einige ergebnissen in Serologischen Beziehung, Centralbl. f. Bact., etc., 1913, 1 Abt. Orig., 141, 104.

7 Fraenkel, C. Untersuchungen zur Entstehung des Keuchhusten, München med. Wchnschr., 1908, 14, 1683.

8 Seiffert, G. Ueber den Bordetschen Keuchhustenbacillus, München med. Wchnschr., 1909, p. 1561.

9 Renaux, E. Le microbe de Bordet et Gengou agent etiologique de la coqueluche, Centralbl. f. Bact., etc., 1914, 1 Abt. Orig., 144, No. 3, 197.

10 Bordet, J. Note Complémentaire sur le microbe de la coqueluche et sa variabilité au point de vue du serodiagnostic et de la toxicité, Centralbl. f. Bact. 1912, Abt. 1, Orig., 146, Parts 2-4, p. 276.

strains of bacilli morphologically similar to *B. pertussis*, but with cultural differences. These strains we call pertussis-like bacilli. Living emulsions were used for the regular inoculations. In the rabbit, antigen extracts similar to those used in the complement fixation test were also tested, as were regular vaccines and sensitized vaccines, for their power to produce agglutinins.

Living cultures of *B. Pertussis* for inoculations were prepared by scraping off a forty-eight-hour culture grown on tube slant on Bordet-Gengou medium in recently isolated cultures, and on coagulated horse blood glycerin veal agar in older strains, and emulsifying in normal salt solution. The dose was graduated according to age of the culture from isolation and to the kind of culture medium used.

The highest virulence for guinea-pigs has been one-half slant of a profuse culture inoculated intraperitoneally. This initial virulence on the blood-veal-agar medium became less after the culture had been grown in successive transplants on this medium for a year. Then one or two slants on coagulated horse blood agar were required to kill a guinea-pig of about 200 strains inoculated intraperitoneally.

The living cultures of influenza bacilli were grown for forty-eight hours on coagulated horse blood agar and then scraped off and emulsified in normal salt solution.

The initial dose of *B. pertussis* and of *B. influenzae* inoculated intraperitoneally into rabbits was from one-eighth to one-half slant. The last dose was five to six cultures on 100 cc Blake bottles.

The *pertussis-like* strains were all on plain veal agar, on which medium they grow abundantly. The emulsions were made in the same way as the others. These strains were very virulent for rabbits, one especially, No. 31, which had to be given at first in doses of  $\frac{1}{100}$  to  $\frac{1}{60}$  of a slant. The last dose was four slants.

The antigen extracts were prepared in the same manner as were those for complement fixation tests, namely, a forty-eight-hour growth of *B. pertussis* on coagulated horse-blood-veal-agar medium was scraped off in distilled water, shaken for two successive days, brought up in the water bath to 56 C and left in the incubator at the same temperature over night, the next day the emulsion was centrifuged and the supernatant fluid rendered isotonic by adding 9 per cent of salt and was injected into the animals.

The dosage of this antigen was  $\frac{1}{4}$  cc intravenously,  $\frac{1}{2}$  cc intraperitoneally, or 1 cc subcutaneously. The dose was gradually increased up to 10 cc. The toxicity of this antigen was tested and it was found that 5 to 10 cc of it killed guinea-pigs 200 gm in weight, inoculated intraperitoneally, in twenty-four hours, 3 cc had no effect.

The vaccines were made by scraping a forty-eight-hour growth of *B. pertussis* on coagulated horse blood veal agar, emulsifying in physiologic salt solution, shaking the emulsion for two successive days and then heating it at 56 C for one and one-half hours. The initial dosage of the vaccine which was usually 15 billions per cubic centimeter strong, was  $\frac{1}{4}$  cc intravenously,  $\frac{1}{2}$  cc intraperitoneally, or 1 cc subcutaneously. Its toxicity was such that 10 cc of a 15 billion strong vaccine killed guinea-pigs of about 200 gm weight, inoculated intraperitoneally, in twenty-four hours, 3 to 5 cc had no effect.

The sensitized vaccines were prepared the same way as the killed vaccines, except that they were shaken only one day, and instead of being heated were agglutinated by 1:100 immune pertussis serum for one hour in the incubator at 37 C and were then placed in the ice-box over night. The next day the precipitated emulsion was shaken up (the supernatant fluid is quite clear) and washed two to three times in physiological salt solution. The dosage of this vaccine was the same as of the killed one, but it was usually 10 instead of 15 billions per cc strong. Its lethal dosage is still being tested in order to gain more explicit data about the comparative virulence of living and sensitized pertussis

organisms Thus far we have found that 1 40 immune rabbit pertussis serum added to 3 cc of a 10 billion per cc strong vaccine prevents the death of 200 gm guinea-pigs, while the control mixtures of normal rabbit serum added to the same amount of emulsion killed the pigs by the next day The emulsions of nonsensitized bacilli in 1 cc doses killed the pigs in twenty-four hours The sensitized vaccine organisms remain alive in the ice-box for two to three weeks, when the growth gradually decreases, on the fifth week only a few colonies are obtained The untreated organism lives in the ice-box about two months More work is being done on the bacterial toxicity of these immune serums

*Technic of Agglutination Tests*—It is of vast importance to obtain homogeneous emulsions, especially for microscopic tests The importance of the culture medium and the subsequent treatment of the cultures for agglutination tests has thus far never been dwelt on in detail by any writer on this subject, except perhaps Bordet<sup>11</sup> himself, and then only on some phases of it *B pertussis* when recently isolated grows only on Bordet-Gengou medium, but after five to six generations, it grows much more abundantly and characteristically on glycerin veal agar 0.4 acid to phenolphthalein, to which horse's blood (1 to 75 to 1 to 100) has been added while the agar is very hot (90) The influenza bacillus also grows excellently on this medium, with the exception that the reaction should be neutral to phenolphthalein Though the pertussis organism grows equally well on the neutral medium, it forms an adherent growth which cannot be separated from the medium and the acid reaction seems to prevent this occurrence The cultures for the tests are taken from a forty-eight-hour growth on this acid medium and allowed to grow for twenty-four hours on 1 to 100 coagulated horse blood veal agar *neutral* in reaction A twenty-four-hour growth usually is not adherent on neutral medium in the first generation from the acid medium The glycerin is omitted for the last growth, as it seems to interfere with the reaction Recently isolated strains, of course, must be grown on Bordet-Gengou medium The growth is scraped off, not washed off, in distilled water and shaken in an electrical shaker for three to four hours A standard emulsion is kept in the ice-box, so that the emulsions are always uniform The serums are diluted with 0.85 per cent salt in 1 to 10, 25, 50, 100, 200, 400 parts, etc Each test tube contains  $\frac{1}{4}$  cc of the diluted serum and  $\frac{1}{4}$  cc of the emulsion, the final dilution being 1 4 The tests are macroscopic with the animal serum and microscopic with patient's serums unless there is enough serum for the macroscopic test The test tubes and hanging drops are put in the incubator at 37 C for one to two hours and readings made, the macroscopic tests are left over night in the ice-box Complete agglutination is designated by ++, incomplete by +, slight by ±

With this technic we have not as yet encountered a self-agglutinating strain on coagulated horse-blood-veal-agar medium and only in the very beginning a few recently isolated strains on Bordet-Gengou medium were slightly self-agglutinating (perhaps they were not shaken long enough) The glassware must be absolutely clean and antiseptics such as mercury chlorid avoided For the examination of patients' serums, one or more strains of *B pertussis* of known agglutinability and one influenza strain are used One-recently isolated strain is grown on rich Bordet-Gengou medium (according to the suggestion from Bordet), the other on our standard medium (coagulated horse

11 Bordet, J, and Sleswyk Serodiagnostic et variabilité des microbes suivant le milieu de culture, Ann d l'Inst Pasteur, 1910, xxiv, 476

blood veal agar) The last medium as a rule gives the most satisfactory results, especially for hanging drops, as it invariably forms a homogeneous mass of entirely separated organisms, and when a reaction occurs it is quite unmistakable

*First Appearance of Agglutinins*—Agglutinins, as a rule, did not begin to appear in the rabbit until after the sixth or seventh inoculation, at least in no higher strength than 1/40 or 1/100 After that, if the animal kept well, the agglutinins continued to rise with each inoculation Most rabbits were sacrificed when they showed from 2,400 to 5,000 titer, which happened usually after the tenth to the twelfth inoculation Some of them might possibly have shown a higher titer if further inoculated

Normal rabbits show agglutination in dilution not higher than 1/25, sheep and goats 1/40 to 1/100, horses up to 100 The sheep and goats seemed to respond more slowly to the inoculations than the rabbits and horses, so they were dropped Two of the three horses—one by intravenous, the other by subcutaneous inoculation—showed agglutinins up to 2,000 after the third and fourth inoculation Two horses are still in the process of immunization

The injection of living cultures intraperitoneally seems to be most conducive to the development of agglutinins in the rabbit, though now and then there is a rabbit found which shows fairly good agglutinations after four to six inoculations With killed vaccines, sensitized vaccines and antigens, the titer has never become as high as with living cultures

Some of the rabbits inoculated with killed vaccines and more of those inoculated with sensitized vaccines and antigens (eight to nine inoculations each) did not develop agglutinins to any extent, though they were markedly immune Thus, five of such rabbits were injected with four to five surface growths of 100 c c bottles without ill effects, while the control rabbits died from the same dose or less (three bottles) the same day or next morning from acute toxemia Two rabbits, more responsive to the vaccines, developed after a few inoculations a comparatively high agglutination titer—up to 1,000 The low titer rabbits were inoculated later with living cultures, and after a few inoculations showed a high agglutinating power The influenza rabbits did not form agglutinins as readily as did the pertussis rabbits, and the titer never reached higher than 1 to 1,600 The accompanying table shows the comparative rise of agglutinins and of complement fixing bodies in rabbits inoculated with *B pertussis*, *B influenza* and pertussis-like bacilli

2 *Specificity of Strains from Whooping Cough Cases*—From Table 3, which shows the agglutinative reaction of pertussis serums

TABLE 1—COMPARATIVE RISE OF AGGLUTININS AND COMPLEMENT FIXATION ANTIBODIES, WITH—  
 INTRAPERITONEAL—

Last Wt Gm	Initial Dose	Last Dose	Strain	After 3d Inoculation		After 4th Inoculation		After 5th Inoculation		After 6th Inoculation		After 7th Inoculation	
				Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C F

PERTUSSIS RABBITS

1,840	1/2 slant	3 slants	P D	†	001	1 40	0003	Rabbit sacrificed after four inoculations					
2,670	1/4 slant	Surface grown of 8 100 cc bottles	55	0	0	0	0	0	005	†	003	1,200	002
1,780	1/8 slant	Surface grown of 4 100 cc bottles	93	0	005	0	004	0	003	0	001	†	0009
1,750	1/4 slant	Surface grown of 4 100 cc 3 bottles	110	0	004	0	0	0	005	†	0004	400	0007
1,880	1 slant on plain veal agar	Surface grown of 4 100 cc 12 bottles	P D	0	0	0	0	40	0	1,200	001	2 000	004
1,565	1/4 slant	Surface grown of 4 100 cc 4 bottles	154	0	0	0	0	0	0	0	0	0	0
2,300	1/2 slant	Surface grown of 4 100 cc 9 bottles	53 M93	0	0	0	0	200	0	1,000	001	2 000	005
2,130	Sensitized vaccine 1/4 cc †	Living culture surface grown 6 100 cc bottles	[ 154 ] [ 155 ] [ 163 ]	0	0	0	0	10	0	†	02	200	002
2,110	Extract "antigen" 1 cc	Living culture surface grown 4-100 cc bottles	[ 154 ] [ 155 ] [ 163 ]	0	0	0	0	0	0	0	0	0	0
2,730	Killed vaccine 1/4 cc	8 cc	[ 154 ] [ 155 ] [ 163 ]	0	003	0	†	400	002	1,600	0005		

INFLUENZA RABBITS

2,350	1/4 slant	Surface grown of 8 100 cc bottles	37	0	0	0	0	0	0	0	0	0	0
1,660	1/2 slant	Surface grown of 5-100 cc bottles	BI2	0	0	0	0	0	0	0	003	0	003
2 080	1/4 slant	Surface grown of 8 100 cc bottles	35	0	0	0	0	0	004	0	003	0	004
2,300	1/8 slant	Surface grown of 11 100 cc bottles	747	0	0	0	0	0	0	0	0	0	003

RABBITS INOCULATED WITH PERTUSSIS-LIKE BACILLUS

05	1,710	1/50 slant	3 1/2 slants	31	0	004	0	003	0	005	0	009	†	009
80	2,365	1/8 slant	6 slants	0	0	0	0	005	0	0	0	006	0	007
65	1,620	1/8 slant	1 slant	1	†	†	1,200	0006	Sacrificed					

\* Injections with living cultures were given once a week, vaccines and antigens were given twice a week till the 4th inoculation, then once a week  
 † Not tested  
 ‡ After injection with living cultures intraperitoneally

SUCCESSIVE INOCULATIONS OF B PERTUSSIS, B INFLUENZAE AND PERTUSSIS-LIKE BACILLUS  
 INJECTIONS

After 8th inoculation		After 9th inoculation		After 10th inoculation		After 11th inoculation		After 12th inoculation		After 13th inoculation		After 14th inoculation		After 15th inoculation	
aglut	C F	Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C F	Agglut	C
PERTUSSIS RABBITS															
†	002	1,000	001	2,400 no more dilutions tried	001	5,200	Rabbit sacrificed								
4,400	001	5,200	Rabbit sacrificed												
2,200	0004	1,000	Rabbit sacrificed												
2,400	0005	2,000	002	2,000	0004	2,400	008	2,400	0008	3,200	002				
0	001	†	001	800	004	1,200	0	1,000	0	800	0				
†	0008	2,400	001	2,400†	0003	4,000	0003	10,000	0003	Sacrificed					
†	003	400	001	2,000†	002	2,400	002	2,400	002	†	002	4,000	001		
0	0	40	003	100	0	†	006	200	0	1,200	008	2,400	†	6,000	001

INFLUENZA RABBITS														
0	0	0	006	0	0	200	001	40	003	400	Test unsatisfactory 0003			
0	001	40	0007	0	003	200	001	200	002	200		40	0005	
0	002	0	0009	200	0003	†	†	0	0009					
200	0008	200	0	†	†	40	0	200	006	200	006	40	†	200\$ 005

RABBITS INOCULATED WITH PERTUSSIS-LIKE BACILLUS												
1,200	009	2,400	001									
0	005	0	003	0	006	0	003					

§ After the seventeenth inoculation this rabbit reacted up to 1 1600, after the eighteenth inoculation it dropped down to 1 400, at the end of the twenty first inoculation the reaction was only 1 200 Complement fixation varied from 0 0008 to 0 0001  
 ¶ Subcutaneously

TABLE 2—AGGLUTINATION TESTS OF PERTUSSIS SERUM WITH HOMOLOGOUS AND HETEROGENEOUS STRAINS—B INFLUENZA, PERTUSSIS-LIKE BACILLUS AND B BRONCHISEPTICUS

Pertussis Strain	Titer of Agglutination in incubator at 37° C for 1½ Hours	40	400	2,000	2,400	2,800	3,200	4,000	5,000	6,000	7,000	8,000	10,000	Control
55	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
M	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
93	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
95	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
P D	8,000	++	++	++	++	++	++	++	++	++	++	++	++	—
163	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
155	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
154	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
109	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
188 R	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
100	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
98	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
110	2,000	++	++	++	++	++	++	++	++	++	++	++	++	—
114	2,000	++	++	++	++	++	++	++	++	++	++	++	+	—
Influenza strain*	Tried in dilution 1 40, 100, 200, 400, etc													
747	—													
37	—													
33	—													
35	—													
Pertussis like strains*														
31	1 40, 100, 200 + — —	+	—	—										
C	1 40, 100, 200 + — —	+	—	—										
10	— — —	—	—	—										
1	+ — —	+	—	—										
Broncho strains*														
155	40, 100 200 ± — —	±	—	—										—
156	± — —	—	—	—										—
97	++ ± ± Control ±	±	±	±										±

\* Pertussis serum

with heterogeneous strains and attempt at cross agglutination with *B influenza*, and pertussis-like bacilli, it would seem that not only do the pertussis strains show no relationship to the pertussis-like strains or to the influenza strains, but that all strains of typical pertussis bacilli belong to one group. This is in marked contrast to the reaction of influenza serums which agglutinate most heterogeneous strains in very low dilutions or not at all. The pertussis-like organisms also show a variation in strains. Thus of the four strains tried, No 31 and No 1 seem to be identical. The others seem to be quite distinct strains. In

TABLE 3—PATIENTS' PERTUSSIS SERA

Weeks Whoop	Agglutination Reactions					Weeks Whoop	Complement-Fixation Tests				
	No of Cases	—	1 40	1 100	1 200		No of Cases	—	+	++	+++
1	13	5	4		4	1	6	4	0	1	1
2	10	0	6	3	1	2	4	3	0	0	1
3	9	1	0	6	2	3	5	0	2	2	1
4	13	2	4	6	1	4	2	0	1	0	1
5	2	1	0	0	1	5	4	1	0	1	2
6	4	0	4	0	0	7	2	2	0	0	0
14	1	0	0	1	0	17	1	0	0	0	1
20	1	1	0	0	0	Convalescent 8	1				1
Convalescent 1	2	1	0	1		Convalescent 5 mos	1				1
Convalescent 8	1	1									
Convalescent 5 yrs	1	1									
Exposed to W O 2 weeks	2		2								
Control sera, adults	58	29	19	10			51	49	2		
Control sera, children (scarlet fever)	10	6	4								

no instance is there cross agglutination of *B pertussis* serum with *B influenza*, even in 1 40. The serum of the pertussis-like bacilli and the influenza serums sometimes agglutinate *B pertussis* in 1 40, but never higher. Of the four strains of *B bronchisepticus* used, none showed any relationship to pertussis agglutinins. The variability of hemoglobinophilic strains has been shown by previous work<sup>12</sup> Absorp-

12 Povitzky, Olga R. Tests of Hemoglobinophilic Bacilli from Conjunctivitis in Regard to Their Virulence and Their Agglutinating Properties, Collected Studies, 1913-1914



*tion tests* verified the supposition gained from the straight agglutination tests, that all pertussis strains belong to one species as far as agglutination reactions are concerned. In order to do these tests, the serum must be saturated by a very thick emulsion, as the least agglutinin not absorbed may be shown markedly by sensitive strains more agglutinable than others, and in this way, obscure the test. One rabbit was inoculated with three strains which we thought might be a little different from each other on account of their varied powers to agglutinate in weak serums, but by absorption tests they proved to have identical agglutinins for themselves as well as for all the other strains<sup>10</sup> tested.

*Variations in Agglutinability of Pertussis Strains*—Though all pertussis strains are practically equally agglutinated by a strong serum, individual strains vary in regard to promptness of response, and with a weak serum heterogeneous strains may show marked difference in the quantity of serum required for a reaction. We have often seen the phenomenon observed by Bordet and others, of the agglutination of heterogeneous strains more strongly than the strain with which the anti-serum was obtained. This characteristic of *B. pertussis* is brought out more clearly by weak serum. Thus, some of our serums from rabbits and goats, after a few inoculations, hardly agglutinated their homologous strains, while they agglutinated a heterogeneous strain up to 1 to 2,000. It is important, therefore, in testing patients' serums to use a strain of known agglutinability (as in typhoid).

The difference in the agglutinability of different pertussis strains was well brought out in the instance of one of our rabbits inoculated with three strains, M, 55 and 93. After five inoculations, its serum agglutinated strains 93 and M and the heterogeneous strain P D up to 200, but not at all Strain 55. After six inoculations, M, 93 and P D were agglutinated up to 2,000, and 55 only very slightly in the first few dilutions. After the ninth inoculation, 55 was agglutinated up to 200, while the other strains showed very strong agglutination up to 2,400. After the tenth inoculation, all four strains (M, 55, 93, P D) showed very strong agglutination up to 2,400 (no more dilutions were tried). After eleven inoculations, all strains were agglutinated up to 4,000 (no higher dilutions tried). After the twelfth inoculation, agglutinins for all three homologous strains and twelve other strains tried were 1 to 10,000 in a trial serum. It would seem that only a very strong serum could overcome the sluggishness of Strain 55. Another strain of this kind is No. 163. Rabbits inoculated with 155, 154 and 163 showed very high agglutination with both Strains 154 and 155 before 163 was agglutinated.

Another interesting feature in the agglutinations of *B pertussis* is that when a mixture of strains is used in making the emulsions for agglutination, the reaction occurs more promptly than when each strain is used alone. Why this occurs we do not yet know. Because of it, we are making comparative tests with a mixture of three or more pertussis strains in emulsion and a one-strain emulsion for testing patients' serums.

According to Bordet,<sup>10</sup> the age of a culture from date of isolation influences the agglutinating property of *B pertussis*. He cites an experiment in which he tested a pertussis serum stored in the ice-box for four years with its homologous strain kept transplanted all these years on Bordet-Gengou medium. No agglutination occurred though this strain was highly agglutinated by the same serum four years ago. The natural conclusion at first was that the serum had lost its potency, but when it was tested with a freshly isolated strain it gave a strong agglutinating reaction. Bordet, therefore, advocates for testing patients' serums for agglutination to use freshly isolated cultures grown on rich blood medium.

In our experience we have found that while freshly isolated strains on Bordet-Gengou medium are quite responsive to a strong serum, the most readily agglutinable strains are a few that were isolated one to one and one-half years ago, and which grow best at present on our standard coagulated horse-blood-veal-agar medium. Of course we cannot predict how much modified these strains may be in four years.

*Relationship of Culture Mediums to Agglutination*—Bordet<sup>11</sup> states that animals inoculated with *B pertussis* grown on Bordet-Gengou medium develop agglutinins for *B pertussis* grown only on the same medium, not for the organism grown on plain agar, and vice versa. He also states that by absorption tests he found that these two agglutinins were not the same.

In testing these experiments, we worked with three mediums: Bordet-Gengou, coagulated horse-blood-veal-agar, and plain veal-agar (only two of our strains grow well on plain agar thus far). When working with weak serums (serums which do not give a prompt reaction in the incubator at one and one-half hours, though they may agglutinate up to 2,400 the next morning) and freshly isolated strains, we were impressed by the truth of Bordet's statements. Thus Horse 1, injected three times with two strains grown on Bordet-Gengou medium, did not agglutinate the same strains grown on coagulated horse blood veal agar, but agglutinated these very strains up to 2,000 when they were grown on Bordet-Gengou medium, but the same serum agglutinated our older agglutinable strain grown on coagulated horse blood veal agar in just as high dilutions. On the other hand, a rabbit

inoculated with a well agglutinable strain grown on plain veal agar after six to seven inoculations, agglutinated up to 2,000 equally well the same strain grown on each of the three mediums. Absorption tests did not seem to bear out the statement that the agglutinins were different. From our experience it would seem that the culture medium influences an agglutinable strain in so far as it affects its growth and best development, not in its production of different kinds of agglutinins. The recent strains grow well only on Bordet-Gengou medium and are, therefore, more agglutinable on this medium than when grown on coagulated horse blood veal agar, on which they grow in the beginning very scantily. The sluggish strains which grow well on either medium seem to be influenced by the culture mediums when tested with weak serums. Thus, the serum of the same horse injected with cultures on Bordet-Gengou medium, which agglutinated an easily agglutinable old strain on coagulated horse blood veal agar, did not agglutinate a sluggish strain on the same medium (though it grows on it profusely) but agglutinated it when it was grown on Bordet-Gengou medium.

A strong serum, therefore, in our experience, agglutinated equally well, though may be not equally promptly, all strains, sensitive and sluggish, no matter on what medium grown.

*Comparative Value of Complement Fixation and Agglutination Tests in the Differentiation of Strains*—Agglutinins as a rule (as mentioned before) did not begin to show in the rabbit in any marked degree till after the sixth or seventh inoculation, while complement fixation antibodies, as seen from the accompanying table, usually appeared after the fourth inoculation, but also showed a higher titer after the eighth to ninth inoculation. Though complement fixation and agglutination outside of the time limit ran quite parallel, namely, most of the animals which show high complement titer show also strong agglutinins, there were rabbits which showed high complement titer and no agglutination, and at times vice versa. Especially was this the case when the rabbit showed a very high complement titer after a few inoculations. Thus Rabbit 28 inoculated with *B. pertussis*, after the fourth inoculation showed a complement titer of 0.0003, and agglutination only 1/40. On the other hand, Rabbit 92 showed complement titer of 0.001 while it agglutinated up to 5,200. Many influenza rabbits showed a high complement titer and very little or no agglutination. On the whole, however, agglutinins in pertussis rabbits, though produced more slowly, were produced more regularly and more surely than were complement-fixing substances.

From our observations we conclude that the agglutination of *B. pertussis* by artificially produced immune serum gives a more clear-cut differentiation from pertussis-like bacilli and from hemoglobino-

phile bacilli than does complement fixation which shows a cross fixation in low dilutions with some of these latter organisms (Olmstead and Povitzky<sup>13</sup>)

3 *The Comparative Value of Agglutination and Complement Fixation in the Clinical Diagnosis of Pertussis*—Serums from 59 cases of pertussis in various stages of the disease were tested for agglutinins. These results, also the results of control serums of adults suffering from different diseases, and of children with scarlet fever are given in Table 3

We see by this table that we cannot depend on agglutination as a positive guide to diagnosis in dilutions up to 1 to 100. If, however, the reaction at 1 to 100 is very prompt (in an hour at 37 C) and complete, it may be considered suspicious, since in none of the controls did the reaction recorded occur quickly. When a reaction occurs in dilutions of 1 to 200, it indicates a probable recent infection with *B pertussis*.

Unfortunately, we did not always get enough serum from patients to test both agglutination and complement fixation, so our comparative table is not of the same cases, but the series of those tested for complement fixation is taken from those quoted in the paper of Olmstead and Luttinger<sup>14</sup> that did not receive vaccines. According to this tabulation, a positive specific complement fixation did not occur quite as frequently in the first week as did agglutination at 1 to 200. On the other hand, out of fifty-one control serums of adults, only two showed a positive reaction by complement fixation while about 33 per cent showed a reaction up to 1:40 by agglutination tests and about 17 per cent showed a reaction 1:100. Control children serums showed in 40 per cent a reaction in 1:40.

Only three out of the fifty-nine pertussis serums showed agglutination with *B influenzae*, two in 1:40 and one in 1:200 in the first week of the whoop.

The control serums showed agglutination with *B influenzae* only in two cases in 1:40, while complement fixation showed fixation with influenza quite frequently.

#### SUMMARY

1 A strongly agglutinating pertussis serum was best obtained in the rabbit by ten to twelve intraperitoneal inoculations of living cultures given at seven-day intervals. Over 95 per cent of rabbits, inoculated in this manner, produced agglutinins, though not in equal abun-

13 Olmstead, Miriam P, and Povitzky, Olga R. The Complement Fixation of Bordet-Gengou Bacillus, Jour Med Research, 1915

14 Olmstead, Miriam P, and Luttinger, Paul. Complement Fixation in Pertussis, THE ARCHIVES INT MED, 1915, xvi, 1

dance Agglutinins are also produced by vaccines, but not as abundantly as by living cultures. Those rabbits which received eight to nine inoculations of vaccine and did not show agglutinins to any large extent, were, nevertheless, markedly immune.

A high titer serum (from 1 4,000 to 1 10,000) always proved to be a quickly acting serum which reacted in from one to one and one-half hours in the incubator at 37 C, sometimes up to 1 8,000, with well agglutinable pertussis strains.

A low titer serum was usually slow in reaction and did not show agglutination till after remaining in the ice-box over night.

2 By agglutination tests, *B. pertussis* strains can be specifically identified from hemoglobinophilic bacilli, pertussis-like bacilli, and *B. bronchisepticus*. In no instance was there cross agglutination between these organisms—at least not higher than 1 40. For identification a strong serum of high titer should be used.

3 By these tests it would also seem that all pertussis strains isolated in our laboratory belong to one group. A strong serum agglutinated all our pertussis strains (twenty-seven in number) equally well though not equally promptly in the highest dilution. Absorption tests (tried in seven most variable strains), proved the supposition gained by the straight agglutination tests.

4 The variation of the agglutinability of pertussis strains with weaker serums depends very much on the age of the culture (dating from isolation) and culture medium. Freshly isolated strains are best agglutinable on Bordet-Gengou medium, older strains on our standard coagulated blood veal agar.

6 A strong serum agglutinates equally well, though not equally promptly, all strains, no matter on what medium grown and how sluggish the strain is.

6 Agglutination tests in clinical diagnosis of pertussis compares favorably with complement fixation only in the first week of the whoop. In the later stages of the disease complement fixation antibodies appear more frequently than agglutinins.

7 Thirty-three per cent of adult nonpertussis serums show agglutination in up to 1 40, 17 per cent in up to 100, 40 per cent of children's nonpertussis serums (scarlet fever cases) showed a reaction in up to 1 40. A dilution of not less than 1 200 is necessary for a practically positive diagnosis of pertussis by agglutination test.

## THE PERMANGANATE REDUCTION INDEX OF CEREBROSPINAL FLUID \*

W O HOFFMAN, M D, AND A B SCHWARTZ, M D

CHICAGO

Children frequently exhibit meningeal symptoms as a manifestation of diseases other than meningitis. The frequency of such symptoms seems to vary in inverse proportion to the age of the child. Thus, infants may show meningeal symptoms in association with almost any disease, while in older children, these symptoms are usually seen only in diseases involving the brain or meninges. Notwithstanding the value of a bacteriological examination, cell count and globulin estimation on spinal fluid, clear fluids are quite frequently obtained on which these examinations throw no light. The great variability in the cytology of the cerebrospinal fluid under the same conditions and the difficulty often encountered in demonstrating the presence of micro-organisms in a clear fluid, make every new aid to diagnosis welcome.

It is particularly in the cases with clear fluids that the permanganate reduction test of Mayerhofer is often of great assistance in diagnosis. The principle of the test, an old one used in water analysis, was adapted by Mayerhofer<sup>1</sup> for the examination of the cerebrospinal fluid. He found that because of their higher content of organic substances, pathological fluids would reduce a larger quantity of permanganate solution than normal fluids. The amount of decinormal permanganate solution, which, boiled for ten minutes in a strongly acid medium is reduced by 1 c c of cerebrospinal fluid, he called the Permanganate Reduction Index. This amount was usually below 2 in normal fluids, Mayerhofer placing the border line of normal and pathological fluids between 2 and 2.3. He applied the test particularly to fluids from patients with tuberculous meningitis, in which a high index was practically the rule.

We have determined this index on the cerebrospinal fluids obtained from patients presenting meningeal symptoms, admitted to the hospital for a number of different conditions. In some of the cases, several determinations were made. As a rule, we confined our

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\* From the Otho S A Sprague Memorial Institute Laboratory of the Children's Memorial Hospital

<sup>1</sup> Mayerhofer, E. Zur Charakteristik und Differential diagnose des Liquor Cerebrospinalis, Wien klin Wchnschr, 1910, xxiii, 651

tests to fluids which were practically clear, also eliminating fluids which contained blood. A few examinations of turbid fluids are given simply to show the constancy of high index values in such fluids. We did not determine the index on various portions of the same fluid, as suggested by Mayerhofer, but used a sample of the entire fluid obtained at one lumbar puncture. The titration was done as soon as possible after withdrawal of the fluid, since, as the author of the test notes, changes occur in fluids on standing which give erroneous results.

While the determination of the Permanganate Reduction Index does not possess the conclusiveness of a specific test, indices usually fall into certain groups, eliminating or suggesting certain diseases. In our series of cases, a reduction index of over 2.5 in a clear fluid, almost invariably indicated the presence of an actual inflammatory process of the brain or meninges, usually a tuberculous meningitis. Other conditions which may, with clear fluid, give high indices, are encephalitis, serous meningitis, and poliomyelitis, practically the same conditions emphasized by Lucas<sup>2</sup> as giving similar cytological findings.

We examined 17 fluids (Table 1) from patients with tuberculous meningitis. Thirty single tests were done on these cases. Of these, 16 had an index above 3, 13 were between 2.5 and 3, only one was below 2.5. This case with an index of 2.3, which is the highest of the border line readings given by Mayerhofer, on a subsequent puncture gave an index of 3.1. While it is true that all of these cases could have been diagnosed without the test, in some cases, the early appearance of the high index is most striking.

A comparison of the cell counts with the reduction index of these fluids shows no definite relationship between the two. The cell counts varied from 30 to 500 per c mm. While, in an individual case, the cell count may show corresponding fluctuations with the reduction index, a comparison of two separate cases shows no such similarity. Thus, in Case 1 with an index of 2.7, the cell count is 30, in Case 22 with an index of 2.5, the cell count is 406. Furthermore, the height of the reduction index seems to vary much more noticeably with the course of the disease than does the cell count. The counts were made on the fresh fluid, employing an ordinary white cell counter, using 10 per cent acetic acid for the dilution. Our results lead us to confirm the inconstancy of cytological findings, as has been noted by Kafka<sup>3</sup> and others.

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2 Lucas, W. P. The Non-Specificity of the Cyto-Findings in the Spinal Fluid in Various Meningeal Conditions, Especially in Children, *AM. JOUR. DIS. CHILD.*, 1911, 1, 230.

3 Kafka, V. Ueber den heutigen stand der Liquordiagnostik, *Munchen med. Wchnschr.*, 1915, 1xii, 105.

TABLE 1—FLUIDS FROM PATIENTS WITH TUBERCULOUS  
MENINGITIS

Case No	Cell Count	Globulin	Index
1	30	+	27
2	125	+	36 38
7	280	+	33
11	325	+	32
17	270	+	25
16	80 150 160	+	30 26
20	187 137 312	+	28 26 27 23
21	110	+	31 25
22	214 406 350	+	25 25
23	175 220 420	+	32 57*
24	175	+	31
25	216 316 500	+	32
32	50 70 100 100	+	28 29 32 28
33	167 211 193 77 205	+	37
37	40	+	29
55	200 218	?	60 43 53
54	?	?	37

\* Slightly turbid



A positive globulin test was a constant finding in these cases, but the quantitative value of this test being only approximate, prevents it from having the same significance as the reduction index

*Other Forms of Meningitis*—The reduction index was determined on the fluids from eight cases of epidemic meningitis. These fluids varied from clear to very turbid. The index was above 3 in all but one fluid, a clear fluid with an index of 2.4. In one case despite a clear fluid, the index remained constantly above 3. A high index may be of value from the standpoint of prognosis, since as pointed out by Mayerhofer, the index in meningococcus meningitis, declines after administration of serum in favorable cases, despite the high reduction value of the serum itself. Two cases of streptococcus meningitis gave indices of 2.7 and 4.8, respectively. The fluid from a patient with pachymeningitis hemorrhagica interna, which was bloody on numerous punctures, and from which the meningococcus was isolated, finally became clear. The fluid showed an occasional red blood cell microscopically. Globulin reaction was positive, cell count 50. The index was 3.4.

*Poliomyelitis*—The index was determined on three cases of acute poliomyelitis. The readings varied from 2.5 to 3.3 in the acute stage, showing a decline coincident with the disappearance of acute symptoms.

*Serous Meningitis and Encephalitis*—In his original article on the reduction index, Mayerhofer particularly emphasized the value of the test in the differentiation of tuberculous meningitis from serous meningitis, or meningismus associated with infectious diseases. Simon,<sup>4</sup> in a critical article, denied its value in these cases. Simon records the index findings in five patients with meningeal symptoms associated with pneumonia. His readings varied from 2.1 to 2.8. In none of these cases did meningitis develop, all but one clearing up. This particular case on postmortem examination showed no pathological changes in the brain or spinal cord. In a subsequent article, Mayerhofer,<sup>5</sup> answering Simon's criticism, stresses the value of determinations made on separate parts of the same fluid, the fluid in tuberculous meningitis giving a higher index in the latter portion, while the reverse is true in serous meningitis. Furthermore, he stated<sup>6</sup> that in mild serous meningitis, a high index, if obtained, remained so for

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4 Simon, G. Zur Untersuchung des Liquor cerebrospinalis nach Mayerhofer, Wien klin Wchnschr, 1911, xxiv, 94.

5 Mayerhofer, E. Kritische Bemerkungen zur Arbeit von G. Simon über meine Methode der Permanganattitration des Liquor cerebrospinalis, Wien klin Wchnschr, 1911, xxiv, 205.

6 Mayerhofer, E., and Neubauer, R. Ueber Meningitis Tuberculosa und Meningitis serosa, Ztschr f Kinderh, 1912, iii, 155.

only a short time. In the malignant cases, he claimed a prognostic value for the high index, illustrated by his Case 119, one of enteritis gravissima in which the index was persistently high. On postmortem examination, a "hyperemia leptomeningum gravis et hyperemia cerebri" was found.

From our experience with the reduction index in such cases, we doubt the advisability of laying down any fast rules in regard to the findings in this condition. Table 2 gives the character of cases we have classified under this heading. The determinations varied from

TABLE 2—SEROUS MENINGITIS AND ENCEPHALITIS

Case No	Index	Symptoms	Diagnosis
14	23	Pain on flexion of neck Hyperesthesia Suggestive Kernig's sign	Septicemia, streptococcic
15	23	Marked rigidity of neck Pain on flexion of head Positive Kernig's sign	Pneumonia, lobar
27	225	Strabismus, rigidity of neck Tense fontanel Positive Kernig's sign	Post operative spina bifida
30	24	Convulsions Restlessness Changed mentality	Tuberculosis of spine and tuber- culosis, pulmon- ary
48	18	Meningeal symptoms	Pneumonia, lobar
49	29 18	Marked meningeal symptoms at first reading Disappearance of these at second reading	Pneumonia, lobar
50	20	"Meningeal symptoms"	Pneumonia, lobar

very low to moderately high. This variation seems to indicate quite a difference in the severity of what we are pleased to call serous meningitis. While routine cultures from the spinal fluid of some of these cases showed no micro-organisms, it seems quite probable that actual changes do occur in the meninges during so-called meningismus associated with the infectious diseases, which account for the variability encountered in the permanganate reduction index. The work of Rohdenburg<sup>7</sup> seems to refute Quincke's<sup>8</sup> original idea that serous

7 Rohdenburg, G. L. and Vander Veer, A. The Spinal Fluid in Pneumonia. Jour. Am. Med. Assn., 1915, lxiv, 1227.

8 Quincke, H. Ueber Meningitis serosa, Samml. klin. Vortr., Leipzig 1893, p. 655.

meningitis is not associated with infection by micro-organisms. All but one of the cases gave borderline readings. Case 49, at the outset showed marked meningeal symptoms. The cell count was 147, of which 71 per cent were polymorphonuclears. The globulin reaction was positive. On the decline of meningeal symptoms, the index became 1.8. It seems reasonable to suppose that the meninges in such a patient actually undergo an inflammatory reaction as found by Voisin.<sup>9</sup>

Cases 27 and 30 came to necropsy. The first developed meningeal symptoms a few days following an operation for spina bifida. Rigidity of the neck, strabismus, a tense fontanel, and a positive Kernig's sign were present. A ventricular puncture was done. Twenty cubic centimeters of clear fluid were removed under greatly increased pressure. The cell count was 3, the globulin reaction was negative. Post-mortem examination showed a marked edema of the brain, marked internal hydrocephalus and hyperemia of the entire brain.

The second case was one of Pott's disease with pulmonary tuberculosis. A few days after admission, the patient had a severe convulsion, following which irregular twitching of the facial muscles occurred for several days. The patient acted peculiarly, was talkative and restless. On lumbar puncture, 20 c c of clear fluid were obtained under pressure. The cell count was 10, globulin negative. Three days later lumbar puncture was repeated with similar findings, except that the Noguchi globulin test showed a faint turbidity. Postmortem examination revealed a hyperemia of the cortex and base of the brain. The French school of pediatricians have noted the great frequency of encephalitis in children, and Lucas has called attention to the occasional similarity of findings in the cerebrospinal fluid of encephalitis and tuberculous meningitis. It is possible that the cases detailed above belong to this class.

In one of the cases of congenital lues which occurred in our series, lumbar puncture was performed following the development of meningeal symptoms. The cell count was 1, the globulin negative, index 2.3. In this instance the actual presence of pathological change was shown only by the index and confirmed by postmortem examination, which revealed an edema of the pia over the entire cortex and base, and an excess of cerebrospinal fluid. On the left side, at the Sylvian fissure, there was an inflammatory exudate. Péhu<sup>10</sup> has recently called attention to the occurrence of encephalitis associated with congenital syphilis, which differs pathologically in no respect from ordinary enceph-

9 Voisin, R. *Maladies des meninges*, Paris, 1912, p. 215.

10 Péhu and Gardere. *Sur un cas d'encephalite aigue avec présence du Tréponème du Niveau des lésions*, Arch. de méd. d'Enf., 1915, xviii, 330.

alitis Several similar cases occurred in our series Clinically they resembled the picture of encephalitis The indices were either borderline or high readings

*Brain Tumor*—In no other condition was the value of the Permanganate Reduction Index as strikingly demonstrated as in a case of brain tumor observed by one of us In this case, the index remained persistently low, while from the clinical picture, the diagnosis of tuberculous meningitis, later, that of solitary tubercle, had been made by several able clinicians The postmortem examination revealed a tumor of the cerebellum

CASE 1—*History*—B N, aged 2½ years, male, was first seen Feb 11, 1914 Family history Father and mother living and well Grandmother had cough, but was never in contact with the child

*Past History*—Nursed one year Repeated "colds" all last winter

*Present Illness*—Has lost 7 pounds in the last seven weeks Has had irregular fever to 101, vomiting "now and then," becoming more marked Bowels costive, chronic headache, no cough Routine examination reveals nothing abnormal except emaciation, no rigidity of neck No Kernig's sign

Blood Examination Red cells, 5 million, white cells, 16,000, hemoglobin, 75 per cent

Feb 14, 1914 Ophthalmoscopic examination shows choked disk Lumbar puncture gives opalescent fluid, 330 cells per cmm, lymphocytes predominant No micro-organisms on culture or smear preparation Pirquet definitely positive

Feb 17, 1914 Slight rigidity of neck Suggestive Kernig's sign on left side, not present on right side Babinski present on left side, not present on right side Marked ataxia Romberg in sitting posture Spinal fluid examination shows same findings as on previous examinations

Feb 18, 1914 Fluid not under pressure Still opalescent Reduction index 17 Physical examination as noted

Feb 21, 1914 Fluid not under pressure Patient better Trace of blood in cerebrospinal fluid, index 18

Feb 24, 1914 Fluid clear, no micro-organisms, index 19 Wassermann on fluid weakly positive Lange test (see Chart, Fig 1)

Feb 28, 1914 Fluid clear Index 19 Lange test (Chart, Fig 2)

March 2, 1914 Fluid clear Blood serum, Wassermann weakly positive Lange test (Chart, Fig 3)

March 9, 1914 Index 15 Lange test (Chart, Fig 4)

March 17, 1914 Index 15 Lange test negative in all dilutions

April 16, 1914 Cerebellar symptoms

April 18, 1914 Index 13 Lange test negative in all dilutions

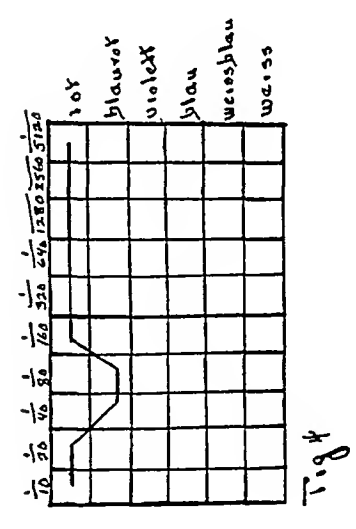
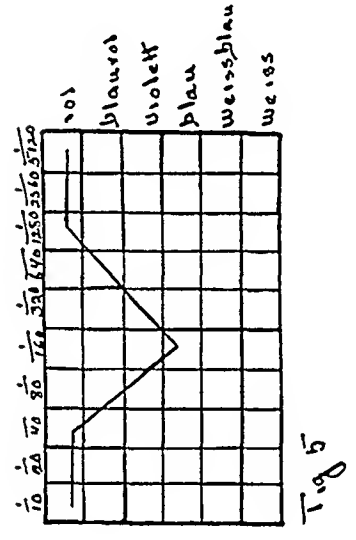
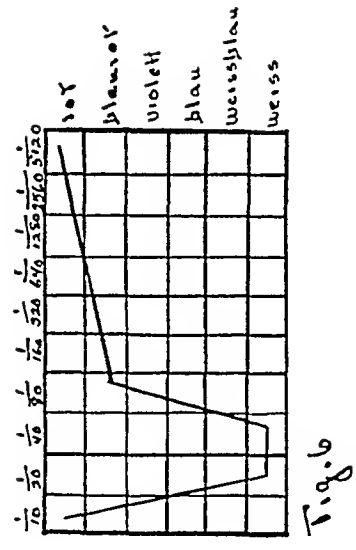
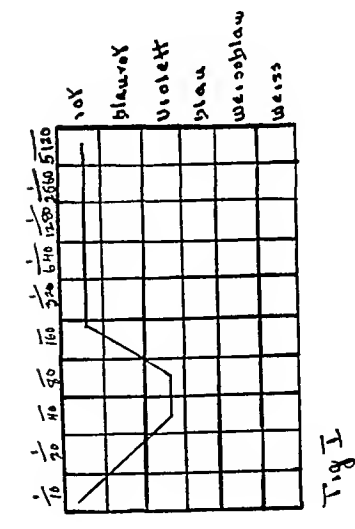
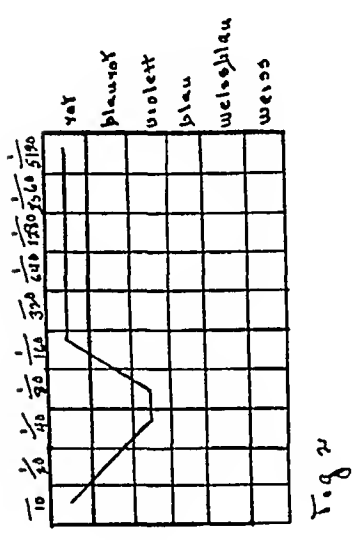
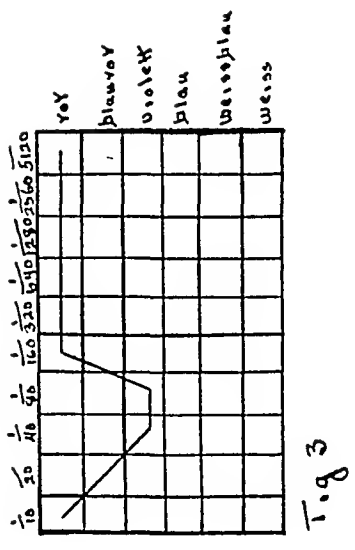
May 9, 1914 Clear fluid Index 17

May 25, 1914 Index 2 Wassermann on fluid negative

*Postmortem Examination*—Anatomical diagnosis, Ependymal glioma Internal hydrocephalus

The following case, though lacking the finality of a postmortem examination, bears a resemblance to the case just noted However, it is quite possible that it is one of solitary tubercle, with low indices, as reported by Mayerhofer

CASE 2—*History*—I L, girl aged 4½ years, was admitted to the Children's Memorial Hospital, Feb 4, 1915



Figures 1, 2, 3 and 4 refer to the case of B N (Case 1)—ependymal glioma—showing the curves of the Lange test Figures 5 and 6 show curves of Lange test in the case of I L (Case 2), of probable tumor

*Family History*—Father and mother living and well, two other children well No tuberculosis in family Mother had one miscarriage

*Past History*—Birth and infancy normal At 6 weeks patient had pertussis followed by pneumonia

*Present Illness*—Patient has been ill since the early part of December, 1914 Vomits once or twice daily Has no appetite Fever present for a few days Occasional chills Constipated Strabismus for four weeks Coughed three weeks ago but not now Restless at night Drowsy and stupid during the day Has lost considerable weight

*Physical Examination*—Patient is a fairly well developed and nourished girl Answers questions "Wants to go home" "Wants mamma"

Eyes Internal strabismus, right eye, pupils alike, react to light and are regular

Tonsils slightly enlarged

Heart sounds irregular Breath sounds normal Abdomen scaphoid Liver felt at costal margin Spleen not felt No adenopathy No paralysis Knee-jerks absent Brudzinski's sign present Kernig's sign not present Slight rigidity of neck

Blood Examination Red cells, 5,240,000, white cells, 9,000, hemoglobin, 80 per cent

Differential Count Polymorphonuclears, 60 per cent, small mononuclears, 38 per cent, large mononuclears, 2 per cent

Wassermann negative

Feb 4, 1915 Lumbar puncture, 30 c c clear fluid, cell count 25, mononuclears predominating Globulin test negative

Feb 5, 1915 Lumbar puncture, 5 c c clear fluid Globulin test negative Index 17

Feb 6, 1915 Von Pirquet negative

Feb 8, 1915 Von Pirquet negative

Feb 8, 1915 Ophthalmoscopic examination Choked disk, both eyes

Roentgen Examination of Chest Negative, except for slight mottling at the lung roots

Lumbar Puncture Ten c c clear fluid, cell count 30, globulin test negative Index 2 Lange test (Chart, Fig 5)

Feb 9, 1915 Sits up all the time Hides eyes Seems depressed No subjective complaints Knee-jerks present both sides No Kernig's nor Brudzinski's sign present Neck is slightly rigid Walks with slight ataxic gait No Romberg sign Babinski's sign present on both sides, left more marked than right No clonus

Feb 15, 1915 Lumbar puncture 20 c c clear fluid, cell count 30, polynuclears and mononuclears equal Globulin test negative Index 19

Feb 19, 1915 Lumbar puncture 8 c c clear fluid Index 2

Feb 23, 1915 Clonus present on right side Knee-jerk absent on right side Clonus absent on left side Knee-jerk increased on left side

Feb 24, 1915 Ophthalmoscopic examination shows less choked disk

Feb 27, 1915 Condition practically unchanged Brudzinski's sign present Knee-jerks present both sides

March 5, 1915 Lumbar puncture cell count 16, globulin test negative No tubercle bacilli demonstrated in any fluids Fluid centrifugalized and 1½ c c of sediment injected intraperitoneally into guinea-pig Lange test (Chart, Fig 6)

March 9, 1915 Patient decidedly worse Marked retraction of head Vomits frequently Sighing respiration Answers when addressed No change in physical examination Temperature normal throughout entire stay Taken home against advice

Death two weeks later

Necropsy on guinea-pig performed five weeks after injection Pig had gained 75 gm No gross lesions of tuberculosis evident

Another very similar case, which ended fatally, occurred in our series The index remained low Guinea-pig injection with the spinal fluid was negative The patient having been taken home against advice one day before death, prevented postmortem examination

Table 3 gives a variety of conditions associated with convulsions occurring in our series The low index values occurring in these cases are self-explanatory

TABLE 3—FLUIDS FROM PATIENTS WITH DISEASES OTHER THAN MENINGITIS

Case	Diagnosis	Index
8	Cystitis	16
9	Little's disease	20
10	Tetany	13
18	Otitis media	21
19	Convulsions (undiagnosed)	19
26	Convulsions (undiagnosed)	21
34	Cerebral syphilis	19
35	Amaurotic family idiocy	19
51	Meningismus (undiagnosed)	16
52	E B (no meningeal symptoms)	16

#### CONCLUSIONS

The permanganate reduction index of Mayerhofer was determined on the spinal fluids obtained from patients admitted to the hospital for a number of different conditions Indices classify themselves into three groups

- 1 Low indices, below 2
- 2 Borderline indices, between 2 and 25
- 3 High indices, above 25

All normal fluids or fluids obtained from patients presenting convulsions or other meningeal symptoms without actual inflammation of the brain or meninges give low indices A few such conditions are tabulated in Table 3 Such an index may be obtained in brain tumor

Borderline indices may occur in the early stage of an inflammatory process, involving the brain or meninges, in serous meningitis, encephalitis or other conditions associated with hyperemia of the brain High indices, if constant, almost invariably indicate an actual inflammatory process of the brain or meninges The two diseases most likely occurring with such indices are tuberculous meningitis and acute poliomyelitis The Mayerhofer test possesses a distinct value in the examination of the cerebrospinal fluid

# TREATMENT OF TYPHOID FEVER BY INTRAVENOUS INJECTIONS OF POLYVALENT SENSITIZED TYPHOID VACCINE SEDIMENT

## STUDIES IN TYPHOID IMMUNIZATION VI\*

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Since the work of Fraenkel<sup>1</sup> in 1893, killed preparations of the typhoid bacillus have been injected subcutaneously as a means of treatment in typhoid fever. Little interest was at first awakened by the suggestive results of Fraenkel except in a discussion of the specificity of his treatment (Rumpf,<sup>2</sup> Kraus and Buswell,<sup>3</sup> Presser<sup>4</sup>). In 1902 Petruschy<sup>5</sup> used a combination of vaccine and immune serum in typhoid, and in 1908 Pescarolo and Quadrone<sup>6</sup> advocated the use of a living, avirulent typhoid culture. Following the interest in vaccine therapy awakened by Wright, increasingly frequent reports on the possible value of typhoid vaccines in typhoid fever have appeared. In 1912 Callison<sup>7</sup> summarized the results obtained by numerous authors, chiefly English and American, in 747 cases, and in 1915 Krumbhaar

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\* For previous studies see THE ARCHIVES INT MED, 1913, xii, 613, 1913, xii, 622, 1914, xiii, 471, 1914, xiv, 662, 1914, xiv, 671. This work was rendered possible by a donation for research from an alumnus of the University of California, and further facilitated by a grant from the Rockefeller Institute for Medical Research.

1 Fraenkel, E. Ueber spezifische Behandlung des abdominal Typhus, Deutsch med Wchnschr, 1893, xix, 985

2 Rumpf, T. Die Behandlung des Typhus abdominalis mit abgetödteten Cultures des bacillus Pyocyaneus, Deutsch med Wchnschr, 1893, xix, 987

3 Kraus, F, and Buswell, H C. Ueber die Behandlung des Typhus abdominalis mit abgetödteten Pyocyaneus Culturen, Wien klin Wchnschr, 1894, vii, 511, 595

4 Presser, L. Ueber die Behandlung des Typhus abdominalis mit Injektionen von Culturflüssigkeiten von Bac Typhi und Bac Pyocyaneus, Ztschr f Heilk, 1895, xvi, 113

5 Petruschy, J. Spezifische Behandlung des abdominal Typhus, Deutsch med Wchnschr, 1902, xxviii, 212

6 Pescarolo, B. and Quadrone, C. Aktiv Immunisation durch subcutane Injektionen lebenden Typhus bazillen bei Eberthscher Infektion, Zentralbl f inn Med, 1908, xxix, 989

7 Callison, J G. The Therapeutic Use of Vaccines in Typhoid Fever. Am Jour Med Sc 1912, cxliv, 350



and Richardson<sup>8</sup> could collect over 1,800 cases reported on by forty authors. It is known that many physicians, and probably an increasing number of them, use vaccines in typhoid because they find they do no harm and they believe them to do some good. The best studied groups of cases treated in this manner, however, give ground for little unrestrained enthusiasm, and certainly no claim that any such type of specific therapy has been attained as is the case in diphtheria and epidemic meningitis. The best that may be said is that the ordinary type of killed typhoid vaccine administered subcutaneously in controlled groups of cases may cause a shortening of the course of the disease, a lower mortality, and perhaps fewer relapses and complications. We purposely refrain from further analysis of the ordinary type of vaccine therapy which has been described, since we are to deal with methods and results which we believe constitute a new era in the specific treatment of typhoid fever.

In the last few months reports on the intravenous injection of ordinary heat-killed vaccine (Thiroloux and Bardon,<sup>9</sup> Kraus and Mazza<sup>10</sup>) and particularly on the intravenous injection of sensitized vaccines (Ichikawa<sup>11</sup>) in typhoid fever, have led us to anticipate a far more hopeful future in combating this disease than has hitherto seemed likely. Before proceeding to a consideration of the results recorded by several authors in actual cases, we may be pardoned for repeating the experimental evidence by which we were led to a practical consideration of this problem before most of these observations were made.

In a previous article in this series Gay and Claypole<sup>12</sup> described a new and specific form of hyperleukocytosis which occurs in immunized rabbits on intravenous reinjection of the specific antigen (bacteria, red blood cells, serum). We found, for example, that the injection of living typhoid bacilli, or of typhoid vaccine in a typhoid immune rabbit, caused the leukocytes to fall in the first two or three hours and then to rise to critical levels that occurred at about the twelfth and again at the twenty-eighth hour. At the latter period leukocyte counts of 150,000 per cubic millimeter were not uncommon, a surprising rise from the normal count of from 8,000 to 12,000, and one that has not been

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8 Krumbhaar and Richardson. The Value of Typhoid Vaccine in the Treatment of Typhoid Fever, *Am Jour Med Sc*, 1915, cxlix, 406.

9 Thiroloux and Bardon. Vaccin Typhique intraveineux, *Centralbl f Bakt Ref*, 1914, lx, 212 (3d ref).

10 Kraus, R., and Mazza, S. Zur Frage der Vakzinetherapie des Typhus abdominalis, *Deutsch med Wchnschr*, 1914, xl, 1556.

11 Ichikawa, S. Mitteil d med Gesellsch, zu Osaka, April, 1912, x, No 5, Abortive Treatment of Typhoid and Paratyphoid, *Sei-I-Kwai Med Jour*, Tokyo, 1914, xxxiii, No 12, p 73, or *Ztschr f Immunitatsforsch*, 1914, xxiii, 32.

12 Gay, F. P., and Claypole, E. J. Specific Hyperleukocytosis. Studies in Typhoid Immunization, IV, *THE ARCHIVES INT MED*, 1914, xiv, 662.

attained, so far as we are aware, by other experimental methods. These hyperleukocytic crises, moreover, are coincident with the destruction of the typhoid bacillus in the immune animal, and would appear to be the cause of it. The same dose of typhoid bacilli in a normal rabbit produces a distinct but markedly lower grade of hyperleukocytosis. We logically regarded the extreme grade of hyperleukocytosis as dependent on the presence of antibodies (tropins) in the immune animal, an hypothesis that we were able to verify by obtaining similar results in normal rabbits by the use of tropinized (sensitized) cultures of *B typhosus*, that is to say, cultures that had been treated with an immune serum. From these experiments it seemed reasonable to express the opinion that the intravenous injection of sensitized typhoid vaccine offered a possibly successful method of treating typhoid fever.<sup>13</sup> As a preliminary to the intended application of the sensitized typhoid vaccine sediment, which we advocate for prophylactic use against typhoid fever,<sup>14</sup> in the treatment of this disease, we tested its curative effect in rabbits that had been made "carriers" of the typhoid bacillus.<sup>15</sup> A few of these animals were apparently freed of the typhoid bacillus by the intravenous injection of the sensitized vaccine, that a majority of them remained unaffected is due to the inaccessibility of the micro-organism in the gallbladder of such carrier rabbits. Further preliminary experiments have shown us that relatively large doses of sensitized typhoid vaccine can be given with safety directly into the circulation of rabbits and monkeys, and even when these animals have been partially immunized against *B typhosus*. The latter condition, owing to the presence of agglutinins, was aimed to simulate the condition in typhoid fever.<sup>16</sup>

On the basis of this experimental evidence accumulated in 1913 and 1914, we were prepared to attempt treatment of human cases, but no opportunity presented itself until early in 1915. Since February of this year we have been privileged to examine over 100 cases of clinically suspected typhoid, to carry out in most of them our own laboratory examinations, and to cooperate in the treatment of the great majority of them in which a diagnosis of typhoid fever could be fully confirmed.

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13 Gay, F. P., and Claypole, E. J. Specific Hyperleukocytosis. Studies in Typhoid Immunization, IV, THE ARCHIVES INT. MED., 1914, xiv, 669.

14 Gay, F. P., and Claypole, E. J. An Experimental Study of Methods of Prophylactic Immunization Against Typhoid Fever. Studies in Typhoid Immunization, V, THE ARCHIVES INT. MED., 1914, xiv, 671.

15 Gay, F. P., and Claypole, E. J. The "Typhoid Carrier" State in Rabbits as a Method of Determining the Comparative Immunizing Value of Preparations of the Typhoid Bacillus. Studies in Typhoid Immunization, I, THE ARCHIVES INT. MED., 1913, xii, 613.

16 It may be of interest to note in this connection that efforts made to produce typhoid carriers in *Macacus rhesus* monkeys by injecting large doses of living culture directly into the circulation have failed.

This study has been made possible by the hearty interest and cooperation of over fifty physicians in Berkeley, Oakland, San Francisco and their environs<sup>17</sup>

We may now proceed to a brief discussion of the results of other investigators who have made use of the recent innovations in the vaccine treatment of typhoid, leaving analysis of details of method and result for comparison with our own records. Recent results with subcutaneous injection of unsensitized vaccine are purposely omitted, however favorable.

*Sensitized Typhoid Vaccines Employed Subcutaneously*—Besredka<sup>18</sup> suggested in 1902 the use of dead or living bacteria that had previously been treated with an immune serum, the excess of which was subsequently removed, as means of producing active immunity without severe reaction. In 1911 Metchnikoff and Besredka<sup>19</sup> on the basis of experiments on anthropoid apes, advocated the use of living sensitized typhoid vaccines as the best prophylactic against typhoid fever and their subsequent results<sup>20</sup> would seem to indicate that they are as good or better than the ordinary vaccine for this purpose. These living sensitized cultures have also been employed subcutaneously in the treatment of typhoid fever during the last few years by several French observers. We find reports by Ardin-Delteil, Negre and Raynaud,<sup>21</sup> Boinet,<sup>22</sup> Deléarde and Leborgne,<sup>23</sup> Sablé,<sup>24</sup>

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17 We wish to express our deepest appreciation to the following physicians who have placed cases at our disposal for this study: Drs. E. N. Ewer, Dudley Smith, George L. Reinle, C. A. DePuy, E. M. Lundegaard, C. A. Queirolo, A. Liliencrantz, Guy H. Liliencrantz, M. L. Emerson, A. F. Clarke, W. H. Irwin, E. A. Majors, H. A. Mackinson, A. M. Shade, C. S. Powell, C. H. Rowe, E. G. Simon, C. R. Krone, F. M. Sylvester, A. S. Kelly, J. M. Shannon, W. H. Streitmann, E. von Adelung and P. F. Abbott of Oakland; Frank W. Simpson, May H. Sampson, Robert Hector, A. M. Meads, L. A. Martin, F. H. Van Tassell, J. J. Benton, J. M. Beuckers, H. S. Delamere, M. F. Toner, R. Paroni, R. T. Legge, H. W. Crane, Sheffield, W. A. Wood, T. C. McCleave of Berkeley; J. K. Hamilton, R. E. Burns and H. M. Pond of Alameda; H. C. Miller, C. A. Wills of San Leandro; H. C. Moffitt, Wm. P. Lucas, Geo. E. Ebright, P. K. Brown, Chas. A. Pauson, Fred G. Burrows, R. L. Wilbur, G. H. Evans, and R. D. MacKinnon, San Francisco, and L. L. Stanley, San Quentin.

18 Besredka, A. De l'immunisation active contre la peste, le cholera et l'infection typhique, *Ann. d. l'Inst. Pasteur*, 1902, xvi, 918.

19 Metchnikoff, E., and Besredka, A. Recherches sur la fièvre typhoïde expérimentale, *Ann. de l'Inst. Pasteur*, 1911, xxv, 193, Des vaccinations antityphiques, *Ibid.*, p. 865.

20 Metchnikoff, E., and Besredka, A. Des vaccinations antityphiques, *Ann. de l'Inst. Pasteur*, 1913, xxvii, 597.

21 Ardin-Delteil, Negre, L., and Raynaud, Maurice. Sur la vaccinothérapie de la fièvre typhoïde, *Compt. rend. Acad. d. sc.*, 1912, clx, 1174, Recherches sur les réactions humérales des malades atteints de fièvre typhoïde traités par le vaccin de Besredka, *Compt. rend. Soc. de biol.*, 1913, lxxiv, 371.

22 Boinet. Vaccinothérapie de la fièvre typhoïde par le virus sensibilisé de Besredka, *Compt. rend. Soc. de biol.*, 1913, lxxiv, 507.

23 Deléarde and Leborgne. *Province méd.*, June 21, 1913, p. 273.

24 Sablé. *Jour. d. sc. med. de Lille*, July, 1913, No. 38, p. 25, No. 29, p. 49.

Netter,<sup>25</sup> Roques<sup>26</sup> and Alfaro,<sup>27</sup> Feistmantel<sup>28</sup> and Garbat<sup>29</sup> have employed other preparations of killed sensitized vaccines. In these, as in the later cases, the criteria of improvement differ with individuals and are hard to compare.

*Unsensitized Vaccine Administered Intravenously*—Several different preparations of killed typhoid vaccine have been tried intravenously but Vincent's polyvalent ether-killed autolysate has been used in the greatest number of cases. Following the brief communication of Thiroloix and Bardon<sup>9</sup> in 1913, articles have appeared by Kraus and Mazza,<sup>10</sup> Kraus,<sup>30</sup> Biedl,<sup>31</sup> Csernel and Marton,<sup>32</sup> Rhein,<sup>33</sup> Reibmayr,<sup>34</sup> Mazza,<sup>35</sup> Holler,<sup>36</sup> Lowy, Lucksch and Wilhelm,<sup>37</sup> Paulick,<sup>38</sup> Ditthorn and Schultz<sup>39</sup> and McWilliams.<sup>40</sup> This intravenous injection of typhoid vaccine gives a definite reaction which if certain limits of dosage are exceeded may be alarming or dangerous. We shall consider this reaction in more detail later.

*Sensitized Vaccine Administered Intravenously*—So far as we are aware, three types of sensitized typhoid vaccine have been employed

25 Netter. Bull et mém Soc méd d hôp, July 24, 1913, p 126

26 Roques. Contribution a l'étude de la vaccinothérapie de la fièvre typhoïde par le virus-vaccin sensibilisé antityphique vivant de Besredka, Theses University of Toulouse, 1913, Ed Ch Dirion

27 Alfaro, A. Rev Soc Med Argentina, 1913, p 683

28 Feistmantel, C. Ueber Prophylaxie und Therapie des Typhus Abdominalis mittels Impfstoffen, Wien klin Wchnschr, 1915, xxviii, 230

29 Garbat, A. L. Sensitized Versus Nonsensitized Typhoid Bacteria in the Prophylaxis and Treatment of Typhoid Fever, Jour Am Med Assn, 1915, lxiv, 489

30 Kraus, R. Bemerkungen ueber Schutzimpfungen und eine Bakteriotherapie des Typhus abdominalis, Wien klin Wchnschr, 1914, xxvii, 1443

31 Biedl, A. (Letter to Paltauf) Zur Vakzinetherapie des Typhus abdominalis, Wien klin Wchnschr, 1915, xxviii, 125, Therapeutische Verwendung von Typhus-Impfstoffen beim Menschen, Prag med Wchnschr, 1915, xl, 53

32 Csernel, E, and Marton, A. Die Therapie des abdominal Typhus mit nicht sensibilisierter Vakzine, Wien klin Wchnschr, 1915, xxviii, 229, Die Behandlung des typhus abdominalis mit nicht sensibilisierter Vakzine, Ibid, p 733

33 Rhein, M. Zur Bakteriotherapie des Typhus abdominalis, Munchen med Wchnschr, 1915, lxii, 427

34 Reibmayr, H. Ueber Impfstoffbehandlung des Typhus abdominalis auf intravenosem Wege, Munchen med Wchnschr, 1915, lxii, 610

35 Mazza, S. Die Bakteriotherapie des Typhus abdominalis, Wien klin Wchnschr, 1915, xxviii, 64

36 Holler, G. Zur Vakzinetherapie des Typhus abdominalis, Ztschr f klin Med, 1915, lxxx, 462, Erfahrungen ueber Bakteriotherapie des Typhus abdominalis, Med klin, 1915, xi, 639 and 668

37 Lowy, R, Lucksch, F, and Wilhelm, E. Zur Vakzinetherapie des Typhus abdominalis, Wien klin Wchnschr, 1915, xxviii, 756

38 Paulick, E. Zur Frage der Typhusheimpfungen, Wien klin Wchnschr, 1915, xxviii, 759

39 Ditthorn, F, and Schultz, W. Zur Antigenbehandlung des Typhus, Med Klin, 1915, xi, 100

40 McWilliams, H. I. Treatment of Typhoid Fever with Typhoid Vaccine Administered Intravenously, New York Med Rec, Oct 16, 1915, p 648

for intravenous administration in typhoid fever Ichikawa,<sup>41</sup> who began this type of treatment (1913), used recent cultures of *B typhosus* sensitized by the serum of patients recovering from typhoid fever and killed, or at least attenuated, by the addition of phenol. A similar method has been employed by Koranyi.<sup>41</sup> A considerable series of cases have since been treated by Biedl,<sup>31</sup> Eggerth,<sup>42</sup> Sladek and Kotlowski,<sup>43</sup> Boral,<sup>44</sup> Holler,<sup>45</sup> Lowy, Luksch and Wilhelm,<sup>37</sup> and F Meyer,<sup>45</sup> who, for the most part, have employed the Besredka living sensitized vaccine.

Any comparison of the results of treatment by these three most recent methods on the basis of percentage benefited, is at best only of suggestive value. As already stated, the criteria on which an estimation of benefit is based vary and no absolute standard is possible, nor do mortality figures offer any conclusive results, but they may be added for completeness since they are at least more definite than any estimated benefit. Since many of the deaths in typhoid are, properly speaking, accidental (hemorrhage, perforations) they cannot be used correctly as criteria of the efficiency of treatment, particularly in those patients that are treated fairly late in the disease where such evolving lesions could not reasonably be affected.

TABLE 1 — SUMMARY OF RECENT CASES OF TYPHOID FEVER REPORTED AS TREATED BY NEWER METHODS OF VACCINE TREATMENT

	Authors	Number Cases	Benefited Per Cent	Mortality Per Cent
1 Cases treated by subcutaneous injection of sensitized vaccine	11	253	57 †	71
2 Cases treated by intravenous injection of untreated vaccine	14	259	63	19 *
3 Cases treated by intravenous injection of sensitized vaccine	8	207	81.8	9.6

\* Due in part to inclusion of a large number of war cases by Paulicek<sup>38</sup> where delayed transportation from the front increased mortality.

† Of 201 cases

This summary would suggest that the best method of treatment of the three would be the intravenous injection of living sensitized vaccine as based on a higher percentage of benefit and lower mortality than the intravenous injection of unsensitized vaccine. Individual reports would

41 Koranyi, A. V. Zur Vakzinebehandlung des Typhus abdominalis, Wien klin Wchnschr, 1915, xxviii, 85.

42 Eggerth, H. Zur Vakzinetherapie des Typhus abdominalis, (Letter published by Paltauf), Wien klin Wchnschr, 1915, xxviii, 126.

43 Sladek, J., and Kotlowski, St. Zur Vakzinetherapie des Typhus abdominalis, Wien klin Wchnschr, 1915, xxviii, 389.

44 Boral, H. Beitr. zur Frage der Typhustherapie mit Besredka-Vakzine, Wien klin Wchnschr, 1915, xxviii, 415.

45 Meyer, F. Spezifische Typhusbehandlung, Berl klin Wchnschr, 1915, lii, 677.

indicate that this difference is really more marked than the summary would show, owing to the fact that the benefit in the third category is more likely to be in the nature of an abortive cure with critical fall of temperature rather than a gradual amelioration and lysis of the fever. Moreover, several authors who have used two or more of the methods do not hesitate unanimously to favor the intravenous over the subcutaneous method and sensitized vaccine over the unsensitized (Holler,<sup>30</sup> Thiroloix and Bardon,<sup>9</sup> Biedl,<sup>31</sup> Meyer,<sup>45</sup> Lowy, Lucksch and Wilhelm<sup>37</sup>)

#### PERSONAL CASES

Owing to the irregular conditions under which our cases occurred in the hospital or home practice of a number of different physicians, it has been necessary for our own records to establish the diagnosis to our own satisfaction by a uniform method. It has also been a pleasure to be able to cooperate in a relatively large number of cases in the differential diagnosis of typhoid fever from other infections, on the basis of laboratory examinations. Although there is no need of defending the value of laboratory methods as aiding in the diagnosis of typhoid fever, it may still be pertinent to express the value of a complete series of negative examinations as tending to exclude typhoid even in the presence of a temporary clinical appearance of the disease. This is particularly important in view of the fact that the laboratory diagnosis in general practice depends almost entirely on a Widal reaction alone, and that often performed in a not wholly accurate manner. We wish, incidentally, therefore, to contribute our laboratory results in the differential diagnosis of typhoid, before considering the treatment of those cases in which the diagnosis was positive.

We have carried out laboratory examinations on 105 cases of suspected typhoid fever which may be subdivided as follows

Total number of cases examined	105
Cases of proved typhoid	65
Cases of typhoid not included as treated	12
Cases treated as suggested	53

*Method of Laboratory Examination*—With few exceptions in the earlier part of the investigation, the routine laboratory examination of each case has been as follows

1 *Blood Culture*—Ten cc of blood, taken from a vein at the elbow, after proper preparation of the skin with iodine, are mixed with 200 cc. of 10 per cent bile broth. In a number of cases the relative intensity of the bacteremia was estimated by plating 1 or 2 cc in melted agar (10 cc). The broth cultures were examined daily to the tenth day or until positive. Organisms of correct morphology for the typhoid bacillus were identified by the usual cultural methods in several sugars (glucose and lactose particularly) and in litmus milk. Final diagnosis of a suspected organism depended on agglutination by an antityphoid serum of high potency.

2 *Widal*—Two to 5 cc of blood were placed in a sterile conical centrifuge tube and allowed to clot. By centrifugalization the serum could then soon

be separated and freed from the blood cells. A series of dilutions beginning 1/10 in a total volume of 1 c.c. of saline was then made running usually to 1/640 or higher when indicated. To each tube there was then added a drop of a thick standard saline suspension of a stock strain of *B. typhosus* grown on agar bottles in large amount and killed and preserved by the addition of 0.1 per cent formaldehyd (40 per cent). A positive reaction is present in a few hours at room temperature in the lower dilutions, but the final results are read from complete sedimentation of the bacteria with clear supernatant fluid on the following day. This type of macroscopic test gives no pseudo reactions even in a dilution of 1/10 and very rarely to a prezone of inhibition. This low dilution therefore may be regarded as diagnostic of typhoid fever (except in vaccinated cases).

In the few cases in which both Widal and blood culture were negative, the typhoid bacillus was sought for in stools and urine.

*Method of Isolation of B. Typhosus from Stools and Urine*—The well known method of smearing direct from stools on successive litmus lactose agar plates was employed. After incubation, suspicious transparent blue colonies were then transferred to agar and sub-cultures made on glucose and lactose media and on litmus milk. Agglutination tests with anti-typhoid serum and paratyphoid "a" and "b" serum of known titer were then made. Enriching with 10 per cent bile broth was also tried, a loopful of the liquid part of the stool or 1 c.c. of urine being added to 5 c.c. of bile broth. Subsequently plates were made as before.

*Cases of Proved Typhoid*—Of the sixty-five cases accepted as typhoid on the basis of laboratory examination, the Widal was positive in sixty (93.7 per cent), including cases in which the examination was made as early as the fifth day. Of blood cultures taken in fifty-eight of these cases there were forty positive (70 per cent) including cases taken as late as the thirty-second day.

*In One Case Only of this Series were Both Widal and Blood Culture Negative*—In this case the diagnosis was based on the presence of *B. typhosus* in the stools.

In this series of sixty-five cases are included two cases of infection due to *B. paratyphosus* "b," one of which was treated and one of which refused treatment by the method to be described.

*Cases of Proved Typhoid That Were Not Treated*—There are twelve cases among the sixty-five of proved typhoid that were not included among the treated patients for the following reasons:

	Cases
No records obtainable from physician	3
Patients died before laboratory diagnosis was complete	2
Post typhoid osteomyelitis	1
Temperature beginning to fall	2
Refused treatment	1
Intravenous injection could not be given	2
Still under treatment	1

These cases are mentioned to emphasize the fact that no choice was exercised in the cases treated. *In every case in which the diagnosis was certainly typhoid the patient was treated if possible except in the*

*instances in which a falling temperature might lead to an unwarranted conclusion of benefit produced by the treatment*

There remain forty patients examined in which the clinical diagnosis of suspected typhoid could not be confirmed by laboratory examinations. It is of interest to note that none of these patients gave a positive Widal in dilution of 1:10 by the method described. The blood cultures were negative in all. In five of the clinically more promising cases the stools and urine were also negative. From the point of view of the accuracy of the laboratory examinations it is of interest to note that on the basis of further laboratory examinations and their clinical course, thirty-six could be excluded as definitely not typhoid. From their interest in the matter of differential diagnosis it may be of value to catalogue these cases as follows

	Cases
Malaria	6
Tuberculosis	4
Brief unknown infections	4
Respiratory infections	4
Trichinosis	2
Influenza	2

and one each of the following. Infection following abortion, erysipelas, tonsillitis, measles, prostatitis, postoperative infection of the nose, appendicitis, pleurisy, coryza, pharyngitis, normal, endocarditis, cystitis, constipation.

There remain then four cases which, on the basis of excellent clinical evidence alone and in absence of confirmatory laboratory proof, may still from one point of view be classed as typhoid. These cases are not included in our treated series on the ground of not being certainly proved typhoid. It may be remarked, however, that two of these patients were treated and both *recovered abruptly* with a single intravenous injection of our vaccine. They would, therefore, if added to our series, simply increase the percentage of favorable results.

We have then a series of fifty-three cases of typhoid fever in which the clinical diagnosis was fully verified by laboratory examination and in which it was possible to carry out specific treatment as intended. Owing to the extremely variable conditions under which these cases have been studied, both in hospitals and homes, it has been manifestly impossible in many instances to carry out as complete examinations from the laboratory point of view as could be desired. The general conduct of the cases from the point of view of diet, hydrotherapy and other palliative measures, we have not been able, or, indeed, wished to control. The variations, then, from the standpoint of general treatment are precisely those which one might expect from the logically different conceptions of the disease found in any group of fifty physicians. The



conduct of the vaccine treatment has, however, owing to the uniform courtesy of those who have allowed us the privilege of this study, been developed from our own experience and the interpretations are again our own. We can only feel that if a similar group of cases could be studied and treated under a uniform set of conditions, that the undoubtedly beneficial results which we attribute to this specific treatment would only be enhanced.

#### METHOD OF TREATMENT

The typhoid vaccine we have used in the treatment of these cases of typhoid fever is one that has already been advocated for the prophylactic immunization of human beings by Gay and Claypole<sup>46</sup>. It consists of the ground sediment of a mixed polyvalent vaccine that has been sensitized by an antityphoid serum and then killed and precipitated by alcohol. From this ground culture the endotoxins are extracted by carbolated saline solution and the remaining sediment of bacterial bodies alone used. On the basis of experimental results this vaccine was found to be superior for protecting rabbits against infection with the typhoid bacillus as compared with other types of vaccine commonly employed, including Besredka's living sensitized vaccine. In the practical use for prophylactic purposes of this vaccine in man it has been shown that it produces less symptomatic disturbance on inoculation (Force<sup>46</sup>) and may be regarded as more protective against typhoid fever in civil communities than several other types of commercial vaccine (Sawyer<sup>47</sup>) as judged by the incidence of typhoid fever among the vaccinated. That the protection afforded by this vaccine employed in civil communities is relative and not so perfect as that hitherto obtained in the United States Army we do not regard as proof that this vaccine may not be as superior to other types of vaccine, including Army vaccine, in practical civil conditions of human infection, as our experimental results in animals would lead us to expect.

This polyvalent, sensitized typhoid vaccine sediment is administered for prophylactic purposes in doses of a suspension of 1/10 mg of dried bacteria, which corresponds to an original bacteria count of about 750 millions. Such a dose when given subcutaneously in a normal individual very rarely produces more than a slight local reaction. For therapeutic purposes we have given doses intravenously ranging from 1/100 to 1/10 mg, most of the doses being between 1/50 and 1/25 mg (150 to 300 million bacteria). Such a dose when administered intravenously produces a series of distinct symptoms which vary

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46 Force, J. N. Institutional Vaccination Against Typhoid Fever, *Am Jour Pub Health*, 1913, III, 750.

47 Sawyer, W. A. The Efficiency of Various Antityphoid Vaccines, *Jour Am Med Assn*, 1915, LXV, 1413.

markedly in intensity with individuals and which are apparently similar in normal and typhoid cases. Although our symptoms are like those described by recent writers who have used the intravenous method for either sensitized or unsensitized dead cultures, it is reasonable to assume that in aliquot parts our vaccine should be less toxic owing to the abstraction of the endotoxins from the ground bacteria. This lesser toxicity seems to have been proved by our results. Although the upper range of doses mentioned may provoke alarming symptoms in the more susceptible individuals, it may be stated at once that in over 150 doses which we have administered no eventual or even temporary harm seems to have been done to the patient. It seems necessary to produce a moderate reaction to bring about the desired results. Before discussing the symptoms that have been noted we may present the record of a typical *severe* reaction produced in a normal individual who volunteered for the purpose.

S B H, male, aged 27, had never had typhoid fever or been vaccinated against typhoid. In good health. Oct 28, 1915, given 180 million sensitized vaccine intravenously.

Leukocyte count before the injection, 6,600, polymorphonuclears, 54 per cent, lymphocytes, 28 per cent; large mononuclears, 18 per cent. Temperature, 100 F.

One half hour after injection patient had a general shaking chill lasting thirty minutes. Patient was not cyanotic but had slight respiratory distress due to muscle spasm. Patient vomited twice after chill was over. Temperature rose gradually to a maximum of 104.4 three hours after injection and then fell to 102.4 at the fifth hour and 97.6 at the tenth hour. It had returned to 99.2 in twenty hours, where it remained. Pulse rose to 120.

Leukocyte counts following injection were as follows:

Hours After	No	Polys Per Cent	Lymphs Per Cent	Large Monos	Eosin
One	4,200	70	22	8	
Three	7,900	88	6	6	
Five	8,800	89	6	5	
Ten	12,000	80	10	10	
Twelve	12,200	75	11	14	
Fourteen	15,400	71	16	13	
Sixteen	16,600	52	15	32	1
Eighteen	14,000	74	8	18	
Twenty	12,000	60	17	23	
Twenty-two	11,000	50	6	44	
Thirty-six	11,600	25	22	52	1
Sixty	11,000	42	27	31	

This reaction in a normal individual is similar to the one produced in a case of typhoid fever, though distinctly more severe than the average.

A composite picture of the train of symptoms that follows the intravenous injection of our sensitized vaccine given in proper dosage is as follows:

A chill occurs beginning in one half hour to one hour and lasting from a few minutes to ten or fifteen. This chill is accompanied by a rise in temperature of 1 to 3 degrees, which reaches its height within three hours after injection, and then falls. There may be a rise of temperature without chill. The rise in temperature is accompanied by a leukopenia as low as 2,000 to 3,000 per cubic millimeter, which may be preceded by a very transitory hyperleukocytosis during the chill. The chill is accompanied by an increase in the pulse rate (say to 120). Slight cyanosis, slight respiratory distress and frequently discomfort may occur.

The fall in temperature reaches normal or subnormal (as low as 94 F per rectum) in about twelve hours. This fall in temperature is accompanied by sweating, which may be profuse and last for several hours, relaxation, and usually general amelioration of such symptoms as headache, delirium and the like. The patient often feels perfectly well and demands food and even when this condition is transitory it would seem to be beneficial. Coincidentally there is a rise in leukocytes which may reach as high as 40,000 and frequently 15,000 to 20,000. This is represented by a relative polymorphonuclear increase of 80 to 90 per cent. This hyperleukocytosis is the more striking in view of the characteristic leukopenia of typhoid. This particular reaction, which we regard as of peculiar significance, was predictable from our experimental results in rabbits and mentioned in a preliminary communication<sup>48</sup>. It has since been touched on by Holler<sup>36</sup> and confirmed fully by McWilliams<sup>40</sup>.

In four instances we feel that the dose administered was too large for the individual case and in such instances there may be vomiting, cyanosis and even symptoms of collapse, with irregular heart action. In one case in which 800 million were given by another's mistake, there was partial collapse and small hemorrhages in the mouth reported.

The possible dangers of the intravenous method of treatment, whether with unsensitized or with sensitized vaccines, have been mentioned by a number of recent authors. It should be stated that unfavorable reports are based on the use of vaccines more toxic than the one we have employed and the criticisms when severe have been based on a very limited experience. Thus Boral<sup>44</sup> had a single patient who died three days after intravenous injection of the Besredka vaccine, in which case the outcome was attributed, for no specific reason, to the vaccine. Sladek and Kotlowski<sup>43</sup> urge caution owing to possible danger of collapse. Deutsch<sup>49</sup> had one patient who died with meningeal

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48 Gay, F. P. Abortive Treatment of Typhoid Fever by Sensitized Typhoid Vaccine Sediment, *Jour Am Med Assn*, 1915, lxxv, 322.

49 Deutsch, F. Zur Vakzinebehandlung des Typhus abdominalis, *Wien klin Wchnschr*, 1915, xxviii, 810.

symptoms five days after treatment Biedl<sup>31</sup> noted increase of epistaxis in two of his patients Csernel and Maiton<sup>32</sup> believe the intravenous injections are contraindicated in hemorrhage, perforation, cholecystitis and cases with irregular heart action It seems evident that with growing experience the danger decreases (Koranyi<sup>41</sup>) and we are inclined to believe with Hollei<sup>36</sup> that the danger lies not so much in the method as in the physician who administers the vaccine Of the authors mentioned, it is interesting to note that only one (Deutsch) really abandoned the intravenous route

It would seem evident from the symptoms that we have described that great caution should be used in choosing the dose to be employed with particular regard to the existence of such existing complications as abnormal cardiac functioning and hemorrhage We have not seen any contraindication in the presence of slight bronchial or broncho-pneumonic involvement and have proceeded cautiously with the treatment in four such cases We have further treated one patient in whom hemorrhage had begun without increasing it

No detailed method of procedure can be prescribed in treating a given case of typhoid fever by our sensitized sediment The best results seem to be obtained by provoking a distinct but not too severe reaction of the type outlined, characterized particularly by a temperature excursion and hyperleukocytosis The dose necessary to produce such a result varies markedly with the individual and with the particular balance already established between the infecting agent and resisting host A single injection may be all that is necessary to restore the individual to an essentially normal condition as judged from the temperature chart, and as has been mentioned, the subjective symptoms follow the fever The temperature may drop to normal following the initial rise and remain there, in which case no further injections are necessary, except perhaps to prevent relapse As a rule, however, the most favorable type of rapid return to normal is a matter of two or three days instead of twenty-four hours, and we have usually waited this longer period before repeating the treatment

We had best leave further discussion of the variations in method of treatment until we have given our results as a whole, together with such correlations as present themselves between the results produced and the blood findings before and after injection

Our cases may be readily divided in respect to results, into three rather sharply defined groups, which we herewith exemplify by the appended type charts (Figs 1-3)

*Group 1 Relatively Unaffected Cases*—This group comprises eighteen, or 34 per cent of our cases Each and all of the successive treatments in these cases, although frequently resulting in temperature

excursion, hyperleukocytosis, and the other symptoms, apparently produce no permanent result so far as shortening the course of the disease is concerned. It is not strictly speaking exact to classify these as "unaffected" for, as mentioned, even the temporary ameliorations in temperature and subjective symptoms we are inclined to regard as beneficial. In a number of these cases it will be seen from the remarks on Table 2 that the fever ran permanently lower after treatment. In other cases the bacteria were diminished or disappeared from the blood. It is, moreover, distinctly to be noted that in none of these cases did the use of vaccine apparently weaken the patient or contribute in any demonstrable way to a fatal outcome when such occurred (Fig 1, Case 47)

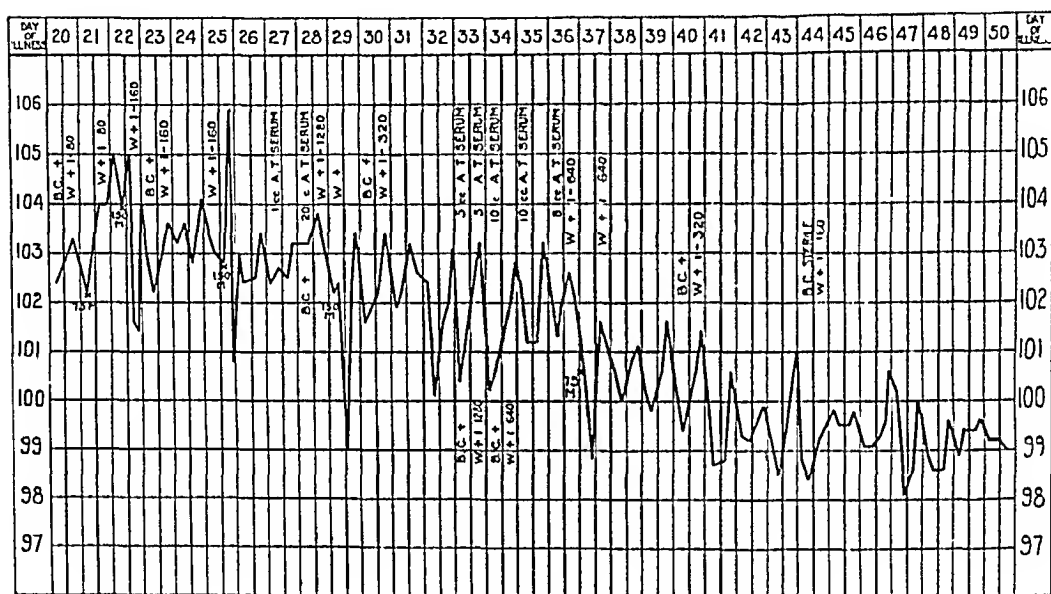


Fig 1—Temperature curve and other data in Case 47. The data in these charts are abbreviated as follows: B.C.=Blood culture, W=Widal, A.T. Serum=Antityphoid serum, 75 M=Sensitized vaccine corresponding to 75 million typhoid bacilli.

*Group 2 Benefited Cases*—Of these cases there were thirteen, or 24.5 per cent in our series. In these cases one or more doses of vaccine led not only to temporary amelioration but to a lytic type of defervescence, the successive drops in temperature being related directly to the vaccine treatments. In cases of this group the duration of the disease was apparently shortened and the course markedly ameliorated (Fig 2, Case 43).

*Group 3 Aborted Cases*—Cases totaling twenty-two, or 41.5 per cent, of our series. In these cases the injection of vaccine led to a more or less critical fall of temperature directly associated with the vaccine injection (Fig 3, Case 35).

TABLE 2—RELATIVELY UNAFFECTED CASES

No	Age	Widal	Blood Culture	Treatment, Day	Number of Treatments	Permanent Normal Temp,* Day	Remarks
2	14	0	0	14	7	Died 32d day	Severe case complicated by laryngeal symptoms Necropsy refused
6	20	+80	+	6	4	38	Severe case White count rose from 8,000 to 21,000 after vaccine treatment
11	7	+	+	5	5	28	Severe case Delirium Abdominal pain
12	5	+	+	7	4	29	Severe case Delirium Abdominal pain
13	25	+	+	15	3	30	Severe case Temperature distinctly lower following vaccine treatment, but course of disease not shortened
14	20	+50	+	15	5	48	Severe case No effect on temperature course
16	45	+	+	12	5	49	Severe case No effect on temperature course
18	30	+320	+	15	1	45	Severe case Temporary effect on temperature course
20	35	0	+	7	2	Died 10th day	Severe Very toxic Patient unconscious when first seen
44	22	+40	+	14	4	52	Moderately severe Slight symptomatic improvement following injection of vaccine
47	62	+80	+	21	6	48	Severe case Blood culture positive to fortieth day of disease
48	14	0	+	21	1	Died 26th day	Severe case Toxic Organism from blood at first inagglutinable Exsanguinating hemorrhage
57	56	+1,280†	+	21	1	Died 27th day	Severe case Temperature normal after vaccine treatment Died six days later from hemorrhage and perforation
61	19	+320	+	11	5	43	Severe case Muscle spasm One colony B typhosus per cc blood on twenty-second day Blood sterile three days later following combined vaccine and serum treatment
66	55	+40	+	14	4	Died 30th day	Severe case Muscle spasm Blood culture positive on twenty-fifth day of disease Three hours after hemorrhage and perforation took place, patient was operated on and perforation closed Patient's general condition was so serious that death followed in spite of there being practically no gross soiling of the peritoneal cavity
72	20	+160	+	11	4	57	Severe case, three colonies B typhosus in 1 cc blood on eleventh day Blood sterile ten days later, following serum and vaccine treatment. Relapse began on thirty-first day, lasting until fifty-seventh day
75	46	+80	+	15	5	35	Severe case, one colony B typhosus in 2 cc blood on nineteenth day Positive with 1 cc blood until twenty-eighth day Blood sterile on thirty-first day and defervescence occurred four days later Hyperleukocytic crisis 17,000 to 18,000 after vaccine treatment
79	19	+320	+	5	4	29	Severe case Toxic and comatose Symptomatically improved by treatment but course not notably shortened
	28	114	95%	13	4	41	

\* A temperature below 100 F by rectum for entire day

† This case with high Widal is not an exception The first injection of vaccine brought the patient's temperature down about three degrees during three days He died three days later of perforation This Widal titer is therefore not included in the average

TABLE 3—BENEFITED CASES

No	Age	Widal	Blood Culture	Treatment, Day	Number of Treatments	Permanent Normal Temp., Day	Duration of Treatment, Days	Remarks
23	21	+160	+	6	2	21	15	Laboratory infection Blood culture positive fourth day Symptomatically well on thirteenth day Afternoon rise in temperature for several days thereafter
32	10	+1,280	+	11	3	32	21	Severe case Very toxic Treatment very cautious because of slight intestinal hemorrhage
38	18	+40	+	9	3	27	18	Severe case Toxic, with muscular spasticity Blood culture positive after three vaccine treatments
39	"	+160	+	11	5	30	19	Severe case Complicated by pyelitis W B C rose to from 10,300 to 25,000 after each vaccine treatment
42	23	+160	+	13	4	26	13	Moderately severe Marked diarrhea W B C rose from 7,800 to 16,250 after vaccine treatment
43	25	+80	0	16	2	26	10	Mild case
46	24	+40	+	11	3	28	17	Severe case Blood culture sterile three days after combined vaccine and serum treatment
49	28	+40	+	15	3	34	19	Severe case Blood culture sterile 72 hours after first vaccine treatment Symptomatically well twenty third day Leukocytes rose from 7,400 to 15,200 after treatment
50	7	+40	+	16	1	28	12	Severe case Toxic and distended
74	26	+160	+	18	3	30	12	Moderately severe Blood culture positive twenty second day Hyperleukocytic crisis of 15,200 after vaccine treatment
81	35	+80	0	11	3	21	10	Mild case
94	30	+80	+	7	3	23	16	Moderately severe Blood culture sterile four days after second vaccine treatment
104	23	+50	+	18	2	28	10	Moderately severe
	21	+182	84.6%	12.4	2.8	27	14.7	

TABLE 4—ABORTIVELY RECOVERED CASES

No	Age	Widal	Blood Cul- ture	Treat- ment, Day	Num- ber of Treat- ments	Perma- nent Normal Temp, Day	Dura- tion of Treat- ment, Days	Remarks
1	70	+		12	1	18	6	Temperature had ranged from 100 to 103 for ten days previous to vaccine treatment
5	80	+180	0	5	3	21	16	Severe case Hyperleukoeytosis of 20,200 following injection of vaccine
10	14	+		10	1	16	6	Moderately severe case
21	53	+640	0	15	2	21	6	Mild
26	14	+		16	2	23	7	Mild
27	28	+160	+	10	3	19	9	Blood cultures sterile 24 and 96 hours after vaccine treatment W B C 4,000 to 14,000
31	19	+320	0	10	1	15	5	Mild
33	15	+320	0	15	2	24	9	Moderately severe
34	6	+320	0	14	1	18	4	Mild
35	28	+160	+	7	2	13	6	Blood cultures sterile 24 and 48 hours after vaccine treatment
40	20	+640	0	14	2	22	8	Mild Accompanied by profuse perspiration
41	8	+160	0	18	2	26	8	Mild
51	5	+20	0	6	1	8	2	Mild Two of three children ill at same time Blood culture positive in one case
52	4	+10	0	6	1	11	5	Mild Two of three children ill at same time Blood culture positive in one case
59	5	+20	+	10	2	16	6	Moderately severe Blood culture sterile four days after first treatment
63	38	+160	0	17	2	23	6	Moderately severe
70	21	+160	+	8	3	18	10	Delirious, severe headache Blood culture sterile 48 hours after first treatment
73	20	+1,280	+	32	3	40	8	Comatose and involuntary Pulse 130 Condition critical
80	14	+160	0	26	1	35	9	Moderately severe
90	8	+40	+	10	2	23	13	Blood culture sterile five days after first treatment None taken between
95	25	+	+	12	2	21	9	Moderately severe
103*	30	+1-40	+	8	3	11	3	Severe
	22 5	260	42%	12 7	2—	20	7 3	

\* Case of paratyphoid "B"



A consideration of our cases as arranged in these three groups brings out a number of interesting correlations (Tables 2, 3 and 4)

We see, for instance, that the treatment was begun on the average on about the same day in all three categories (12 to 13) and that the average age of the patients was nearly the same. The first group of "Relatively Unaffected Cases" differs distinctly from the "Abortively Recovered" ones in that the blood cultures were positive in over twice as many cases in the first (95 per cent as compared with 42 per cent) and again in the fact that the Widal was much lower on the average in the unaffected cases than in the aborted cases (1 to 114 and 1 to 260).

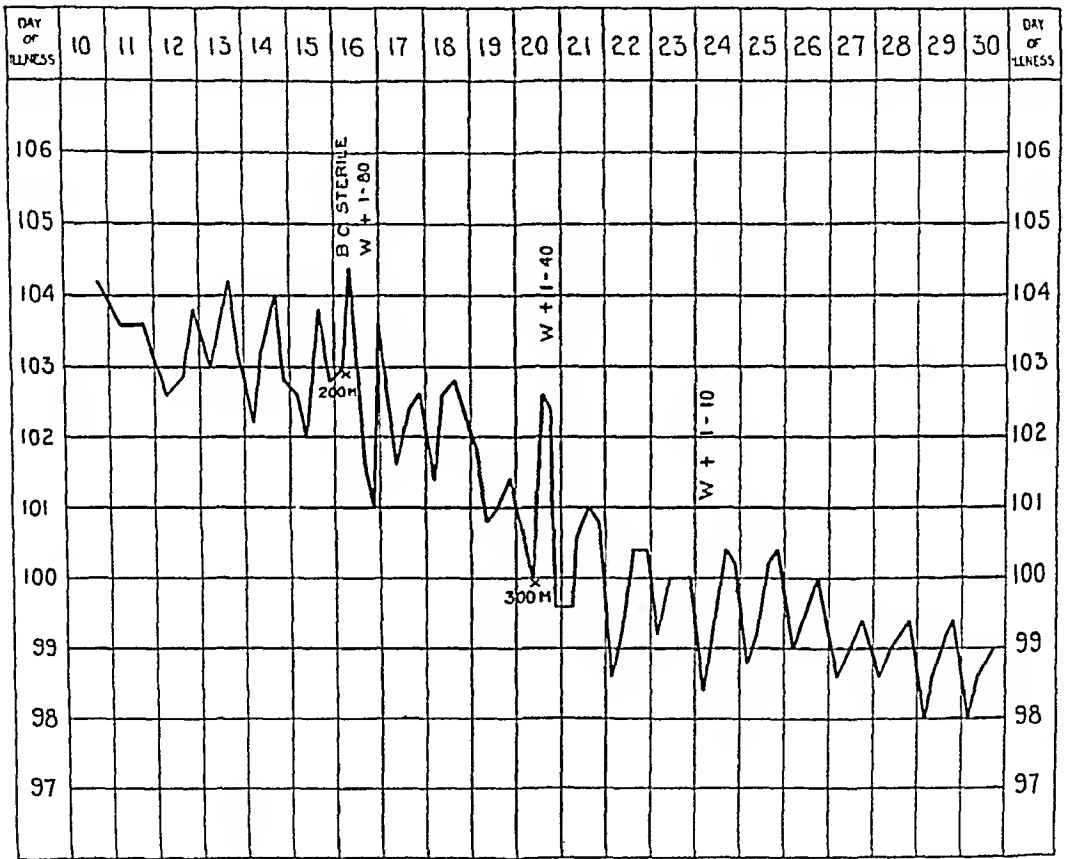


Fig 2—Temperature curve and other data in Case 43

The benefited cases (Group 2) lie intermediate between the two, having nearly as high a percentage of blood cultures as Group 1 and nearly as high a Widal average as Group 3

There is little doubt that the number of typhoid bacilli in the circulating blood bears a distinct relation to the severity of the course of the disease, and the persistence of positive blood cultures indicates an unfavorable outcome (see particularly Schottmuller,<sup>50</sup> Jochmann<sup>51</sup>)

50 Schottmuller, H Die Typhosen Erkrankungen, Handb der inn Med, 1912, I, Mohr and Staehelin

51 Jochmann Lehrbuch der Infektionskrankheiten, Springer, Berlin, 1914

Conversely the disappearance of the bacteriemia early in the disease is a favorable indication. From such facts we should expect to find the third group of cases in a general way milder than Group 1.

Whereas it is impossible to judge what the outcome of any one of our cases would have been without treatment, certain impressions of the severity of the cases *before treatment* in relation to the outcome may be of interest (Table 5).

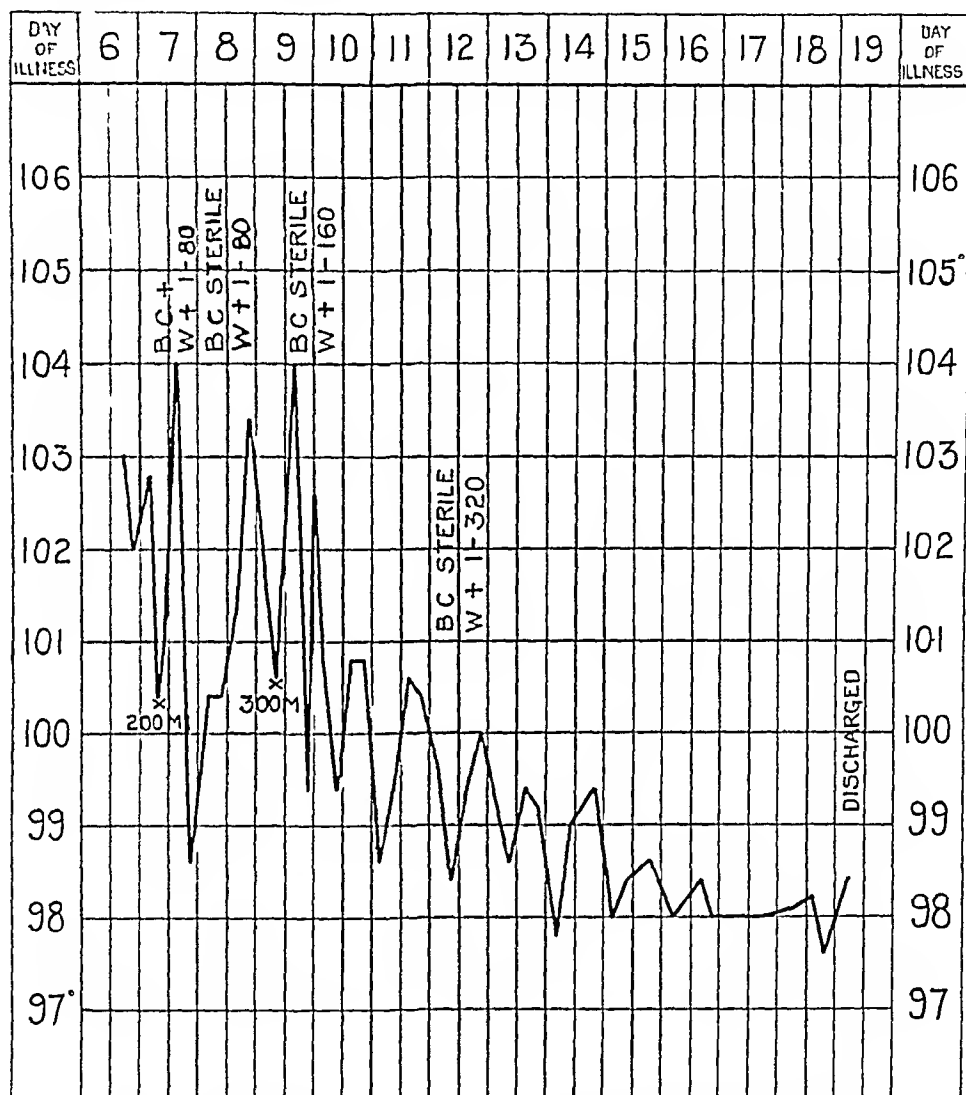


Fig 3—Temperature curve and other data in Case 35

TABLE 5—GENERAL CONDITION OF THE CASES BEFORE TREATMENT

	Severe	Moderate	Mild
Group 1, unaffected	15	3	0
Group 2, benefited	6	5	2
Group 3, aborted	4	7	11

It is evident that the milder cases were more likely to be favorably affected by treatment than the severe ones. In this connection it may be wise to forestall criticisms that might be made to our interpretation of the abrupt recoveries as due to the injection of vaccine. It may be suggested by clinicians with an extensive experience in typhoid fever

that they have seen cases (usually a case) in which the temperature fell by crisis in typhoid fever without treatment. We have been able to find little detailed account of such a course in the literature. McCrae<sup>52</sup> in his carefully analyzed series of 1,500 cases noted a critical fall in two cases only (0.1 per cent). He further notes a mild form of typhoid in 44 cases (3 per cent). These figures added or separately, may be compared with our 41.5 per cent of rapid recoveries. Of further significance is the direct relation of the vaccine injection to the result

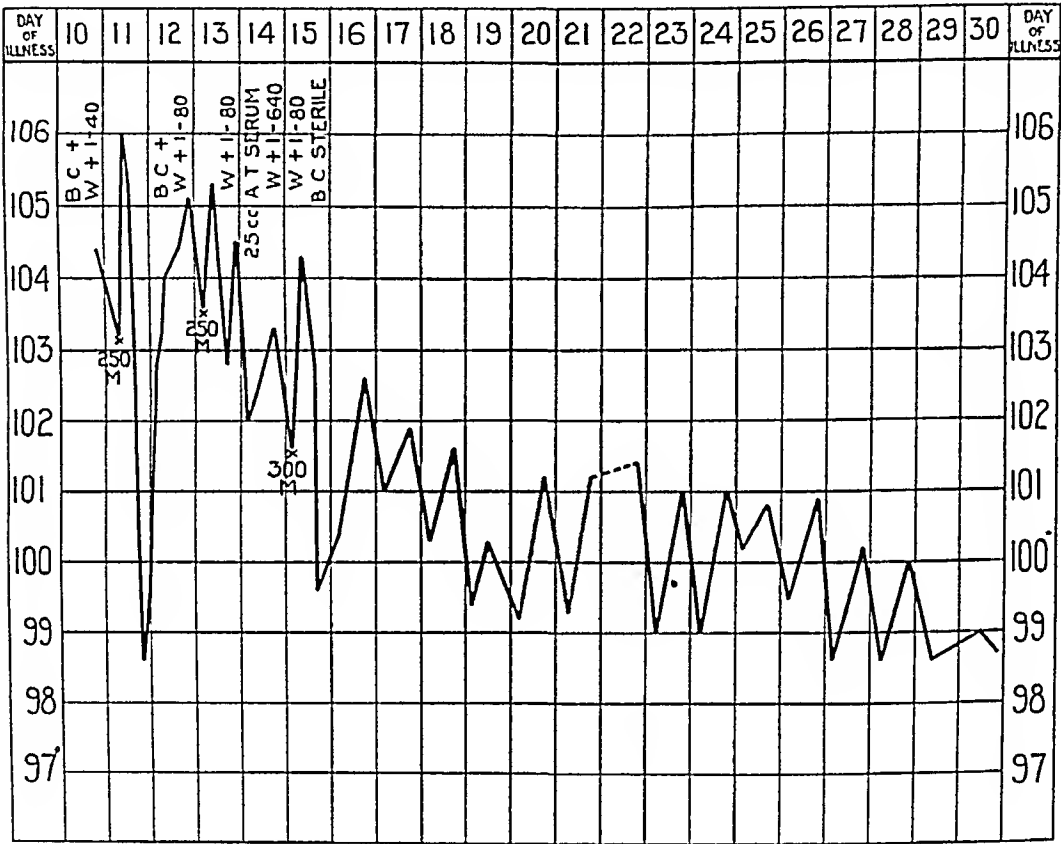


Fig 4—Temperature curve and other data in Case 46

produced and the fact that the average duration of the specific treatment until a *permanent* normal temperature was reached was a little over seven days

In this connection it may be of interest to contrast the average duration of the disease in the three categories as compared with McCrae's figures (Table 6)

TABLE 6—DURATION OF DISEASE AS CONTRASTED WITH MCCRAE'S FIGURES		
Group 1, unaffected	41	days
Group 2, benefited	27	days
Group 3, aborted	20	days
Real average	27.6	days
Average of McCrae's 1,500 cases	31	days

52 McCrae Osler's System of Medicine, Ed 1, II, 70

The relative intensity of the Widal reaction in the favorably affected cases as compared with the others seems to us of peculiar significance. It may be taken as an indication of the degree of successful response that the patient has made to the infection. We do not wish to assume that the agglutinin titer is any true measure of resistance, but it often runs parallel to those antibodies that are responsible for tipping the balance in the patient's favor. Our conception of the recovery that is favored by the intravenous injection of sensitized vaccine would be that it is due first to a hyperleukocytosis produced in maximum degree by the use of tropinized bacteria, and secondly to the action of the patient's own antibodies on the circulating bacteria. Such a conception to be proved would necessitate an estimation of the patient's tropins in relation to results produced rather than the agglutinins. The establishment of an accurate method for such determinations is at present engaging our attention.

A further corollary of this hypothesis should show that the bacteria in the patient's blood disappear or diminish in the presence of a hyperleukocytic rise and the simultaneous presence of suitable antibodies. This was found to be the case in rabbits in the experiments of Gay and Claypole. Although it has not been possible to take an extensive series of blood cultures in many of our cases, our results show that in ten cases positive blood cultures became sterile in from one to three days after injection of vaccine. We contemplate a more extensive series in this direction. In addition to diminishing the bacteremia or actually sterilizing the patients, as would seem to be the case in many of our abortively recovered cases, the injection of sensitized vaccine in the majority of cases is accompanied by an increase of the Widal titer which, as we have seen, is of favorable prognostic significance.

In view of the probable mechanism of recovery in typhoid fever induced by the intravenous injection of sensitized vaccine, it might seem reasonable in those cases associated with a low Widal titer in which less favorable results may be anticipated, to supply the necessary antibodies artificially. This could be done by the use of an immune serum. One is not impressed with the results hitherto attained in the serum therapy of typhoid (Chantemesse,<sup>53</sup> Rodet,<sup>54</sup> Rodet and Lagriffoul,<sup>55</sup>

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53 Chantemesse, M. Toxine typhoïde soluble et serum antitoxique de la fièvre Typhoïde, *Prog. med.*, 1898, Series 3, vii, 245.

54 Rodet, A. Die Serotherapie beim Typhus, *Handb. der serum Therapie*, A. Wolf-Eisner, München, 1910.

55 Rodet, A., and Lagriffoul. La Serotherapie de la Fièvre Typhoïde, *Presse med.*, 1910, xviii, 969.

Ludke,<sup>56</sup> Andriescu and Ciuca,<sup>57</sup> and Koenigsfeld<sup>58</sup>) We have no certainty whether such a serum should be antiendotoxic, or according to our own working hypothesis, largely tropic While waiting for further experimental evidence on this point we have felt justified in certain of our cases, particularly in those with a low Widal, in giving intravenous injections of the serum of goats that had received repeated subcutaneous and intravenous injections of several strains of living *B typhosus* Whereas the result with such serums has not been in many instances striking, it has at all events shown the harmlessness of goat serum even when given in fairly large quantities intravenously

Fresh goat serum was first shown to have no hemolytic or hemagglutinative effect on human blood corpuscles In each case where intravenous injection was intended 1 c c of goat serum (either normal or immune) was given subcutaneously twenty-four hours previously to avoid possible anaphylactic shock In all eight cases were given intravenous injections ranging from 20 to 95 c c In no instance was any untoward immediate symptom noted, and in only one case was a slight urticaria found subsequently This latter finding may be contrasted with the usual results which follow the intravenous injection of large amounts of immune serums from the horse (Cole<sup>59</sup>) In all instances, as expected, the infusion of a relatively considerable amount of antiserum caused an immediate rise of the agglutinins in the patient and in several instances the serum injection alone seemed followed by a symptomatic improvement and slight defervescence

In one case (Fig 4, Case 46) which we trust will not prove to be exceptional, two injections of vaccine in a patient with low Widal and positive culture early in the disease (tenth day) were followed by persistent positive cultures and only temporary temperature fall The administration of 25 c c of antityphoid serum intravenously followed the next day by a third dose of vaccine, led to sterilization of the blood stream and immediate defervescence In this case at least it seems evident that the cure was due to the mixed serum and vaccine treatment

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56 Ludke, H Die Serumtherapie des Abdominal typhus, Munchen med Wchnschr, 1912, xxv, 907, Die Behandlung des Abdominal typhus mit Intravenosen Injektionen von Albumosen, Munchen med Wchnschr, 1915, xxviii, 321

57 Andriescu, C, and Ciuca, M De l'action du Serum antityphique de Besredka sur l'evolution de la fièvre Typhoide, Ann de l'Inst Pasteur, 1913, xxvii, 170

58 Koenigsfeld, H Ein neues Prinzip der Serumtherapie bei Infektionskrankheiten mit besonderer Berücksichtigung des Typhus abdominalis, Munchen med Wchnschr, 1915, lxii, 253

59 Cole, R Pneumococcus Infection and Lobar Pneumonia, THE ARCHIVES INT MED, 1914, xiv, 56

## FATAL CASES

It will be seen from Table 2, comprising our relatively unaffected cases, that there have been five fatal cases in our treated series, or a little over 9 per cent, which does not differ from McCrae's large series with the same mortality. Of course no mortality average is of great significance in so small a series as our own. It is to be noted that a disproportionate number of our cases have died from the "accidents" of typhoid, if we may so call them. There was hemorrhage in three cases, two of which were followed by perforation. These two complications should account for death in 40 per cent of the cases according to McCrae. In our own series they represent 60 per cent of the fatalities. It should be noted that in two of these cases the treatment was not begun until the twenty-first day. True typhoid toxemia was the cause of death in only one of our cases (20). Case 2 was toxic, but probably died of some laryngeal complication, necropsy was refused.

## RELAPSES

There have been five relapses in our series (9 per cent), somewhat lower than McCrae's average of 11.4 per cent. It should be noted that two relapses have occurred in our cases listed as abortively recovered after discharge from the hospital, both promptly responded to a single reinjection of vaccine. The early discharge of the patient we believe had a distinct influence on the occurrence of these relapses. During the latter part of our series we have followed the intravenous treatments with a series of three subcutaneous injections of the vaccine in the dosage ordinarily employed for prophylaxis (1/10 mg = 750 million). In twelve cases in which this treatment has been fully carried out there have been no relapses, whereas the five relapses occurred in forty-one cases in which no such treatment was employed or completed. These subsequent subcutaneous injections may be followed by slight rise of temperature.

## SPECIFICITY OF TREATMENT EMPLOYED

In view of the relative success that has been reported by means of certain nonspecific methods of treating typhoid fever, it may be well to express our conception of the relation of our method of treatment to such methods.

Early in the history of the treatment of typhoid by vaccines Rumpf<sup>2</sup> questioned the specificity of the results claimed by Fraenkel<sup>1</sup> on the ground that he had obtained similar favorable effects by the use of preparations of *B. pyocyaneus*. That such results were at least relatively less effective would seem to be shown from the subsequent work of Kraus and Buswell<sup>3</sup> and Presser.<sup>4</sup> Kraus<sup>60</sup> has obtained abortive

<sup>60</sup> Kraus, R. Ueber Bakteriotherapie akuter Infektionskrankheiten, Wien klin. Wchnschr., 1915, xxviii, 29.

cures in typhoid by the use of colon vaccines. Ichikawa has cured paratyphoid, as we did, by sensitized typhoid vaccine. Ludke<sup>55</sup> has mentioned favorable results by the simple use of a deuterio-albumose. Letulle and Mage<sup>61</sup> and Gay<sup>62</sup> have treated cases of typhoid by means of a preparation of colloidal gold (colibiase). We believe such favorable results, which we are quite ready to accept, are in reality in perfect harmony with each other and with our own choice of treatment. All of these substances including colloidal gold<sup>63</sup> produce hyperleukocytosis, particularly when injected into the circulation. Leukocytic extracts probably act in the same way in those cases in which they are undoubtedly effective. Any of these substances could therefore be expected to cure a percentage of cases of typhoid owing to the dual mechanism of a hyperleukocytosis plus antibodies in the patient.

Intravenous treatment by means of sensitized typhoid bacilli differs from the above methods in two ways:

1. Owing to the fact that the injected protein is sensitized or tropinized, the response on the part of the leukocytes is much more intense and effective (Gay and Claypole<sup>12</sup>).

2. Typhoid vaccine aids in building up the active immunity of the patient against typhoid fever as no other preparation can.

#### SUMMARY

This article deals with the study of 105 cases of suspected typhoid fever in which we were allowed to examine the patients through the great courtesy of a number of physicians in Alameda and San Francisco Counties. Thorough laboratory examinations in most of these cases by blood cultures and Widal tests and in a number the search for the typhoid bacilli in the stools and urine, offer certain facts of interest in the differential diagnosis of typhoid fever. In 65 of the 105 cases the diagnosis of typhoid fever was made from both clinical and laboratory data. In these 65 cases the Widal was positive in 60 (93.7 per cent) and as early as the fifth day, the high percentage of results being due, in a large measure, to the method employed, namely, the use of the macroscopic method and a formaldehydized culture of the typhoid bacillus. Of the blood cultures taken in 58 cases there were 40 positive (70 per cent), including a case first seen on the thirty-second day. In only one case of the 65 were both Widal and

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61. Letulle, M., and Mage. *Traitement la Fièvre Typhoïde par l'or colloïdal en injections intraveineuses*, Bull. de l'Acad. med., Paris, 1914, lxxii, 421.

62. Gay. *Un Traitement pratique de la fièvre typhoïde aux armées*, Presse med., March 4, 1915, p. 67.

63. See discussion by Robin and Chantemesse in loc. cit., Ref. 60.

blood culture negative, which case was diagnosed by the presence of *B typhosus* in the stools

Of the 40 cases excluded as not being typhoid fever on a laboratory basis, 36 could ultimately be excluded on both clinical and further laboratory examination. There remain 4 cases which on clinical evidence alone may have been typhoid, but which are not included in our series owing to the fact that laboratory proof was lacking. It may incidentally be remarked that 2 of these cases were treated by the method described, with abrupt recovery. Of the 65 cases it was impossible for various reasons that are stated, to treat 12. The remainder of the cases, however, were all treated without choice.

There remain, then, a series of fifty-three cases of typhoid fever in which the diagnosis was absolutely certain both on clinical and laboratory grounds. We have not attempted to influence the ordinary symptomatic treatment of these cases, which differs as much as might be expected in a group of over fifty physicians. The patients, moreover, were cared for under varying conditions in private homes and hospitals, some of them even without the attention of a trained nurse. This variation in care and location of the cases had undoubtedly an effect on the mortality and has made thorough laboratory examinations, such as leukocyte counts at frequent intervals, impossible in all the cases.

The mortality in these cases has been precisely what one would expect under the best hospital conditions (McCrae), namely 9 per cent, which we regard as suggesting that, under uniform conditions, with our method of treatment the mortality would have been less than the average. The mortality has been composed, to a large extent, of what may be termed the "accidents" of typhoid, namely 60 per cent of the deaths by hemorrhage or perforation.

Our method of treatment has consisted in the intravenous injection of 1/50 to 1/25 milligram (150 to 300 million bacteria) of a sensitized, polyvalent, killed typhoid vaccine sediment prepared after the method of Gay and Claypole. This injection gives rise to a series of symptoms characterized particularly by a chill, rise and fall of temperature and leukopenia followed by hyperleukocytosis. The fall of temperature with its attendant hyperleukocytosis leaves the patient at least temporarily benefited, and the benefit and normal temperature may be permanent. Thus in 66 per cent of the cases a distinct benefit was obtained, as shown by lowered temperature, disappearance or amelioration of subjective symptoms and an apparently accelerated recovery. In 41.5 per cent of this 66 per cent the recovery was of an abortive form with a critical fall of temperature and a permanent normal temperature established within a few days. This permanent normal tem-



perature was reached on an average seven days after beginning treatment in these cases. There remains, however, 34 per cent of cases which are classified as relatively unaffected. We regard this classification as underestimating the beneficial results for reasons given. In none of the cases did the use of the vaccine have any apparent harmful effect on the case, although in four, in which too large a dose was used, the symptoms were somewhat alarming.

A series of subcutaneous injections following the intravenous treatment apparently aids in preventing relapses.

We regard the mechanism of benefit and cure in these cases which were affected by the treatment as due to a combination of specific hyperleukocytosis and the presence of antibodies (tropins?) in the patient's blood. The injection of vaccine could be shown in a number of cases to be followed by the disappearance or diminution of bacteremia and usually also by an increase in the Widal. In those cases which did best the Widal was originally high and those cases which showed the least effect had the low Widal. The cases judged as "mild" before treatment began did better on the whole than those regarded as "severe." There were, however, a number of severe cases which showed abrupt recovery or benefit.

On the hypothesis that successful results are due to the strength of the antibodies already established in the patient, we have ventured in severe cases with low antibody content, to combine with the vaccine treatment the intravenous injection of considerable amounts of typhoid immune serum from goats. These cases, although few in number, suggest that this type of treatment with further elaboration might increase the percentage of favorable results.

We regard the use of sensitized vaccine as being better for intravenous injection than plain typhoid vaccine or less specific methods of treatment that have been suggested by other authors, owing to the fact that sensitized typhoid vaccine produces a specific form of hyperleukocytosis of maximum degree (Gay and Claypole), and may also be shown to be followed by an increase in active immunity of the patient against the disease.

# THE INTERPRETATION OF A POSITIVE NITROGEN BALANCE IN NEPHRITIS<sup>1</sup>

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It has been the practice of clinicians for many years to treat cases of nephritis by means of a dietetic therapy, in which the various forms of nitrogen-containing food have been much restricted. One of the several reasons for curtailment of protein in the dietary has been that a damaged kidney cannot readily excrete the end products of protein metabolism, as measured by the nitrogen, and that a distinctly harmful result follows such a retention. The determination of a nitrogen balance in nephritis has been considered one of the valuable tests of the ability of the kidney to eliminate this substance. In the interpretation of this procedure, three factors have been considered essential:

1. An accurate determination of the food nitrogen
2. An accurate determination of the output of the nitrogen in the urine and feces

3. A constant intermediary nitrogenous metabolism. The first two of these demands are readily fulfilled, the third is vague in its requirements and no definite standards have been established for it in clinical medicine. Studies in nephritis are largely based on the criteria set by Ascoli and von Noorden. These authors acknowledge that there may be either an increased protein catabolism or an assimilation of ingested nitrogen within the body which may cause an apparent loss or gain of nitrogen to the organism for which the kidney is in no wise responsible. The problem which has to be solved is, how are such possible changes to be eliminated? Ascoli and von Noorden<sup>1</sup> in their own words make the following suggestions in this connection:

Ascoli. These observations are based on the experience that an individual who is receiving a medium or at least a sufficient amount of food with not too

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<sup>1</sup> Submitted for publication, Nov 16, 1915

<sup>2</sup> From the Medical Clinic of the Johns Hopkins Hospital

1. Ascoli. Wir gehen bei diesen Beobachtungen von der Erfahrung aus, dass der Mensch bei einer mittleren oder eben genügender Nahrungszufuhr mit nicht allzu geringem Eiweissgehalte innerhalb 24-stündiger, noch besser aber mehrtägiger Beobachtungszeiten ziemlich genau so viel Stickstoff—in Form der verschiedenartigsten Schlacken—in Harn und Kot ausscheidet, als mit der Nahrung, vor allem mit dem Eiweiss, eingeführt wird. Bleibt unter diesen Umständen die Ausfuhr gegen die Einfuhr merklich zurück, so kann es sich zwar bei heruntergekommenen Personen um Fleischansatz aus dem eingeführten Eiweiss handeln, meist kann aber ziemlich unbedenklich angenommen werden,

low a protein content, will excrete in the urine and feces in a twenty-four-hour, or better still, several-day period of observation, an amount of nitrogen in the form of the various waste products approximately equivalent to that taken in. If the amount excreted is markedly less than the quantity ingested, it is possible that some of the retained material is utilized to build up the tissues, in the case of individuals who are emaciated, but, as a rule, it may be assumed without question that particular nitrogenous residues which should be excreted are being retained in the blood, in the organs, and by chance, in edematous accumulations as waste nitrogen.

Von Noorden. It is evident that statements of nitrogen elimination in the urine are of value only when the amount ingested, as well as the quantity excreted in the feces, is considered and if the observations are sufficiently prolonged. The diet must be at least fairly constant and the nitrogen content must be easily ascertained. If the observations do not attain these standards, then they are deserving of consideration only when extreme deviations from the normal occur, as in the occasional cases cited by Frerichs, Bartels and S. Rosenstein, in their publications.

These statements are not precise and allow of much latitude in their interpretation. To give them more concrete form we may compare them with the actual fulfillment in a given case. Von Noorden claims, in the above quotation, that in order to set aside changes in the intermediary metabolism, the diet must be fairly constant, the observation must be carried on over a considerable period and that if these conditions are not fulfilled, then the changes noted must be very striking in order to be of value. In a patient,<sup>2</sup> a boy of 11 years, whose data were considered extremely important as being the first case in which protein destruction was demonstrated in uremia, the period of observation was ten days, the nitrogen content of the food was 7.8 gm on every day excepting two, when no food whatsoever was taken, and the result of the nitrogen balance for the whole period was a loss of 20.8 gm, or a little over 2 gm of nitrogen per day. This may be considered a very lax interpretation of the criteria set for such experiments. They are, however, characteristic of the manner in which they have been adhered to by many authors who have reported results with nitrogen balances in clinical work. The cases which are reported here all fall within the limits set by these figures and show how thoroughly inadequate they are in rendering the course of intermediary nitrogenous metabolism a negligible factor.

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dass eine Anstauung von zur Ausscheidung bestimmten Schlacken im Blute, in Organen, allenfalls in sich ansammelnden Oedemenstatthat. Vorlesungen über Uramie, Jena, 1903, p. 166.

Von Noorden. Es ist klar, dass die Angaben über N-Elimination nur Wert haben, wenn sie die Bestimmung der Nahrungszufuhr und des Kotstickstoffs einschliessen und die Versuche nicht allzu kurz sind. Zum mindesten muss die Diät einigermaßen konstant und ihr N-Gehalt leicht zu berechnen gewesen sein. Erfüllen die Versuche diese Bedingungen nicht, so verdienen sie nur Beachtung, wenn geradezu extreme Abweichungen vom Gesunden vorlagen, wie in einzelnen Fällen, die Frerichs, Bartels, S. Rosenstein in ihren Handbüchern zitieren. Von Noorden. Handbuch der Pathologie des Stoffwechsels, Berlin 1906, I, 978.

2 Von Noorden. I c in Note 1, p. 972.

The method of Folin and Denis<sup>3</sup> for the total nonprotein nitrogen of the blood, which was the one used in the present series, opens the way to a deeper knowledge of nitrogen metabolism. With three data, the nitrogen intake, the nitrogen output, and the amount of waste nitrogen in the blood, at our command, the trend of intermediary protein metabolism, as well as the power of the kidney to eliminate nitrogen, become apparent. It has previously been shown that, in experimental uranum nephritis, at least, an increased protein catabolism takes place and may be detected by these means.<sup>4</sup> The present observations deal with the second phase of this subject, namely, the influence that the assimilation of ingested nitrogen may have on the interpretation of the nitrogen balance.

The patients investigated in this connection were all cases of chronic interstitial nephritis of moderate severity. The first four cases studied were at the outset put on a "low protein" diet and subsequently on a "high protein" diet. These diets were as follows:

#### LOW PROTEIN DIET

*Breakfast* Sherry, 30 c c Baked apple, stewed prunes, orange "Hominy cornstarch cereal"<sup>5</sup> Cream, 15 c c

*Dinner* Sherry, 30 c c Potato, baked or mashed String-beans, cabbage, carrots, lettuce, onions, tomatoes, cucumber pickles Fruit cornstarch pudding, fruit tapioca pudding

*Supper* Same as dinner

Salt, sugar and butter may be used as desired and need not be weighed. All other food eaten must be weighed or measured.

#### HIGH PROTEIN DIET

Bread, coffee, cream, milk, cocoa made with milk, eggs, oatmeal, broth, baked or mashed potato, roast beef, beefsteak, chopped beef, chicken, custard, rice pudding

Salt, sugar and butter may be used as desired and need not be weighed. Whisky and sherry may be used to make up eggnogs, etc., and need not be measured. All other food eaten must be weighed or measured. Measure the milk and cream separately from the coffee, oatmeal, etc., when serving them.

Make the diet as full as possible, allowing much meat and broth.

Each patient was given sufficient food from these lists to satisfy the appetite. The amounts to be consumed were weighed, duplicate determinations for nitrogen were made on every sample of food. The average nitrogen values thus obtained were as shown in Table 1.

These figures vary somewhat from those given in the standard food tables. They also do not agree with analyses made on the food from the same hospital kitchen a few months previously. It would seem that for very accurate work samples of the actual food consumed must

<sup>3</sup> Folin and Denis Jour Biol Chem, 1912, xi, 527

<sup>4</sup> Mosenthal THE ARCHIVES INT MED, 1914, xiv, 844

<sup>5</sup> Two-thirds hominy, one-third cornstarch

necessarily be analyzed and that previous analyses or dietary tables cannot be relied on absolutely. It will be seen from the protocols that the nitrogen intake on the days of low protein diet was between 1.54 and 4.30 gm, while on the high protein diet it varied from 16.83 to 47.37 gm. The intake in each individual, however, was much more constant on the days of similar diet than these maximum variations for all the cases indicate.

TABLE 1—NITROGEN CONTENT OF THE FOODS USED IN THE HIGH AND LOW PROTEIN DIETS

Article of Food	Percentage of Nitrogen
Bread	1.47
Coffee	0.03
Cream	0.41
Milk	0.53
CEREALS	
‡ "Hominy cornstarch"	0.13
Oatmeal	0.36
FRUITS	
Baked apple	0.04
Orange	0.16
Stewed prunes	0.14
VEGETABLES	
Cabbage	0.16
Carrots	0.10
Lettuce	0.24
Onions	0.17
Cucumber pickle	0.10
Baked potato	0.48
Mashed potato	0.40
Stringbeans	0.23
Tomatoes	0.23
DESSERTS	
Blackberry cornstarch pudding	0.05
Prune cornstarch pudding	0.07
Custard	0.92
Soft custard	0.81
Apple tapioca pudding	0.02
Peach tapioca pudding	0.06
Rice pudding	0.72
MEAT PRODUCTS	
Broth	4.00
† Chopped beef	3.36
Cold roast beef	5.40
† Beefsteak	3.90
Chicken	5.67
‡ Eggs	2.13

‡ Two-thirds hominy, one-third cornstarch

† These nitrogen determinations were made on uncooked food, all the other determinations on prepared foods

‡ Eggs are the only article of food listed the nitrogen value of which was not actually determined. The figures were taken from standard food tables of Atwater and Bryant (Bulletin 28, revised edition, U. S. Department of Agriculture)

## METHODS

The Kjeldahl method was used for the quantitative determinations of nitrogen in the food, urine and stools. In the first four cases, the stools were collected in composite periods, corresponding to the duration of high and low protein diets. They were marked off by the alternate ingestion of charcoal and carmin. The fecal material was dried in evaporating dishes, after the addition of a small amount of sulphuric acid, ground in a mortar and thoroughly mixed before being analyzed. In the last two cases, the stools were collected in twenty-four-hour periods, without demarcation, and aliquot portions of the thoroughly mixed moist feces were used for analysis. The procedure of Folin and Denis<sup>6</sup> was employed to obtain the figures for nonprotein nitrogen of the blood. The original method was adhered to, except that a combined process of distillation and aeration was substituted for aeration alone.

TABLE 2—DATA OF CASE 1

Diet	Weight, Lbs	Nitrogen, Gm in 24 Hours					Nonprotein Nitrogen of the Blood, Mg per 100 c c
		Urine	Feces	Total Output	Intake	Balance	
Low protein	147½	6.00	75	6.75	3.33	— 3.42	31.8
Low protein	146½	4.50	75	5.25	3.13	— 2.12	
Low protein	148½	3.36	75	4.11	3.17	— 0.94	
Low protein	146½	3.15	75	3.90	3.37	— 0.53	
High protein	147	6.23	82	7.05	26.46	+19.41	29.7
High protein	147½	6.16	82	6.98	31.25	+24.27	
High protein	148	11.38	82	12.20	32.20	+20.00	
High protein	147	5.59	82	6.41	21.68	+15.27	
High protein	146½	10.20	82	11.02	24.03	+13.01	37.0

In each case there was a slight loss of nitrogen on the low protein diet. On the first day of this diet the deficit was rather large in one instance. This was, in all probability, due to the elimination of nitrogenous waste products which had previously been retained. On the high protein diet there was very marked nitrogen retention in all the patients. Thus, considering the whole period of observation, the nitrogen balance is distinctly positive. (See Table 6.)

In spite of this, the nonprotein nitrogen of the blood remained at a comparatively low level—33.9 to 38.1 mg per 100 c c—exceeding the normal by only a slight margin. (The upper normal limit of total nonprotein nitrogen of the blood has been variously placed at 26<sup>6</sup>, 30<sup>7</sup>, 32<sup>8</sup>, 37<sup>9</sup> and 40<sup>10</sup> mg per 100 c c.)

6 Folin and Denis Jour Biol Chem, 1913, xiv, 29

7 Frothingham and Smilie THE ARCHIVES INT MED, 1915, xv, 204

8 Tileston and Comfort THE ARCHIVES INT MED, 1914, xiv, 620

9 Folin and Denis Jour Biol Chem, 1914, xvii, 487

10 Foster THE ARCHIVES INT MED, 1915, xv, 356

How are these results to be interpreted? Under the given conditions, the usual conclusion has been that the kidney is insufficient and that consequently the urinary nitrogen cannot keep pace with the quantity ingested. In such instances it is supposed that the retained nitrogen circulates in the body as nonprotein nitrogen and manifests itself by a rise in its concentration in the blood. It is, therefore,

TABLE 3—DATA OF CASE 2

Diet	Weight, Lbs	Nitrogen, Gm in 24 Hours					Nonprotein Nitrogen of the Blood, Mg per 100 c c
		Urine	Feces	Total Output	Intake	Balance	
Low protein	98¾	6 10	1 27	7 37	1 93	— 5 44	36 0
Low protein	97½	2 48	1 27	3 75	2 24	— 1 51	
Low protein	98¾	2 89	1 27	4 16	2 34	— 1 82	
Low protein	97¾	1 43	1 27	2 70	1 87	— 0 83	
High protein	97¼	6 07	1 53	7 65	16 83	+ 9 18	29 7
High protein	97	7 75	1 53	9 33	26 71	+17 38	
High protein	97	7 38	1 63	8 96	22 54	+13 58	
High protein	97½	9 80	1 53	11 38	26 35	+14 97	
High protein	97¾	7 68	1 53	9 26	19 13	+ 9 87	33 1

TABLE 4—DATA OF CASE 3

Diet	Weight, Lbs	Nitrogen, Gm in 24 Hours					Nonprotein Nitrogen of the Blood, Mg per 100 c c
		Urine	Feces	Total Output	Intake	Balance	
Low protein		2 73	1 41	4 14	1 82	— 2 32	21 2
Low protein	112	2 55	1 41	3 96	1 68	— 2 28	
Low protein	111¾	2 41	1 41	3 82	1 98	— 1 84	
Low protein	110½	1 77	1 41	3 18	1 54	— 1 64	
High protein	111	4 29	0 94	5 23	18 34	+13 11	25 4
High protein		7 45	0 94	8 39	17 11	+ 8 72	
High protein	112¾	9 05	0 94	9 99	19 22	+ 9 23	
High protein	112	10 70	0 94	11 64	20 97	+ 9 33	
High protein	111¼	8 19	0 94	9 13	19 73	+10 60	33 9

necessary to ascertain, approximately, at least, to what height the retention of a given amount of nitrogen should raise the figure for waste nitrogen in the blood if this hypothesis is to be supported.

It is known from the work of Marshall and Davis<sup>11</sup> that urea is evenly distributed throughout the body, except in certain tissues, as the

<sup>11</sup> Marshall and Davis Jour Biol Chem, 1914, xviii, 53

fat, bone, cartilage, teeth, outer layers of the skin, etc., which do not take up urea. Since the greater part of the nitrogen of the food—approximately 85 per cent—is excreted as urea on a moderately high nitrogenous diet, a substantial increase in the nonprotein nitrogen of the blood would be expected if the kidneys did not eliminate this substance sufficiently rapidly to keep pace with its production. It is at the present

TABLE 5—DATA OF CASE 4

Diet	Weight, Lbs	Nitrogen, Gm in 24 Hours					Nonprotein Nitrogen of the Blood, Mg per 100 c c
		Urine	Feces	Total Output	Intake	Balance	
Low protein	136	17.16	0.75	17.91	3.69	—14.22	46.6
Low protein	135	8.83	0.75	9.58	2.15	—7.43	
Low protein	135½	5.88	0.75	6.63	2.86	—3.77	
Low protein	137	3.03	0.75	3.78	4.30	+0.52	
High protein	139	7.10	1.47	8.57	20.52	+11.95	29.7
High protein	140	7.31	1.47	8.78	32.76	+23.98	
High protein	138½	12.87	1.47	14.34	27.02	+12.68	
High protein	139¼	12.56	1.47	14.03	32.63	+18.65	
High protein	139¼	11.77	1.47	13.24	47.37	+34.13	37.1

TABLE 6—SUMMARY OF OBSERVATIONS ON THE NITROGEN BALANCE AND THE NONPROTEIN NITROGEN OF THE BLOOD

	Case 1	Case 2	Case 3	Case 4
Nonprotein Nitrogen of the Blood, Mg per 100 c c				
At beginning of observation	31.8	36.0	21.2	46.6
At end of low protein period	29.7	29.7	25.4	29.7
At end of high protein period	37.0	38.1	33.9	37.1
Nitrogen balance in grams for				
Low protein period	—7.0	—9.6	—8.1	—24.9
High protein period	+92.0	+65.0	+51.0	+101.4
Total period of observation	+85.0	+55.4	+42.9	+76.5

time not accurately known how the other nitrogenous products destined for urinary excretion are distributed in the body. Many of these are evidently stored in the tissues in much greater concentration than they are found in the blood<sup>12</sup>. However, these materials are probably being held for further use in the body and may be considered in a vastly different light from those which are to be excreted. For the purposes

<sup>12</sup> Van Slyke and Meyer Jour Biol Chem, 1912, xii, 399, 1914, xvi, 197, 1914, xvi, 213. Folin and Denis Jour Biol Chem, 1912, xi, 87, 1912, xii, 141.



of determining the theoretical values of the nonprotein nitrogen of the blood in this series of cases, in which it was supposed that the nitrogen output should have equaled the intake, the total quantity of retained nitrogen has been assumed to be equally distributed in the body. From the figures given by Marshall and Davis it is found that in an individual weighing 70 kilos the retention of 30 grams of urea is equivalent to a rise of 40 mg per 100 c c in the urea of the blood. Applying the same principles to the total non-protein nitrogenous products which are supposed to be excreted by the kidneys, it is seen that for every gram of nitrogen retained, the non-protein nitrogen of the blood should be increased 1.33 mg per 100 c c. According to these calculations, in the cases presented here, if none of the retained nitrogen were assimilated or stored, and all of it circulated as waste nitrogen, because the kidneys did not excrete it, the figures shown in Table 7 would be obtained.

TABLE 7—THEORETICAL AND ACTUAL VALUES OF NONPROTEIN NITROGEN OF THE BLOOD RESULTING FROM NITROGEN RETENTION

	N Gms Retained During High Protein Period	Theoretical Value of Nonprotein N of Blood, Mg per 100 c c *	N Gms Retained During Whole Period of Observation	Theoretical Value of Nonprotein N of Blood, Mg per 100 c c †	Actual Value of Nonprotein N of Blood, Mg per 100 c c
Case 1	92.0	152.0	85.0	144.8	37.0
Case 2	65.0	116.2	55.4	109.7	38.1
Case 3	51.0	93.2	42.9	78.3	33.9
Case 4	101.4	164.6	76.5	148.4	37.1

\* These figures represent the values obtained for nonprotein nitrogen of the blood at the beginning of the high protein period plus the theoretical increment due to retained nitrogen.

† These figures represent the values obtained for nonprotein nitrogen of the blood at the beginning of the observation plus the theoretical increment due to retained nitrogen.

Even an extremely large error in these theoretical calculations would not invalidate the conclusion that the retained nitrogen was not circulating as waste nitrogen but had been assimilated or stored by the body tissues. In normal individuals a similar storage or assimilation of nitrogen may occur on a high protein or a high calory diet, as was shown by Wolfe,<sup>13</sup> Luthje,<sup>14</sup> Luthje and Berger,<sup>15</sup> von Noorden and Krug,<sup>16</sup> and Bornstein.<sup>17</sup> In the absence of carbohydrate food, such an assimilation of nitrogen is difficult to obtain.<sup>18</sup> Frothingham and

13 Wolfe, Quoted by Lusk. Science of Nutrition, 1909, p. 124.

14 Luthje. Ztschr. f. klin. Med., 1902, xlv, 22.

15 Luthje and Berger. Deutsch. Arch. f. klin. Med., 1904, lxxxv, 278.

16 Von Noorden and Krug. Arch. f. Anat. u. Physiol., Physiol. Abt., 1893, p. 371.

17 Bornstein. Pflüger's Arch. f. Physiol., 1901, lxxxi, 540, Berl. klin. Wchnschr., 1898, xxxv, 791.

18 Lusk. Science of Nutrition, 1909, Chapter vii.

Smillie<sup>19</sup> report instances of nephritis exhibiting the same phenomena as those discussed here

TABLE 8—DATA OF CASE 5

Nitrogen Gm in 24 Hours					Nonprotein Nitrogen of the Blood Mg per 100 c c
Urine	Feces	Total Output	Intake	Balance	
11 15	1 46	12 61	11 56	— 1 05	29
8 57	1 31	9 88	14 08	+ 4 20	
13 21	0	13 21	13 23	+ 0 02	
12 79	3 28	16 07	15 11	— 0 96	
6 67	1 96	8 58	19 09	+10 51	
7 25	2 75	10 00	19 91	+ 9 91	
11 00	0	11 00	13 93	+ 2 93	
10 46	2 53	12 99	19 89	+ 6 90	
13 55	1 71	15 36	19 12	+ 3 76	
12 20	1 91	14 17	11 99	— 2 18	26
12 65	1 80	14 45	14 50	+ 0 05	
12 76	0 97	13 73	15 15	+ 1 42	
13 80	0	13 80	17 56	+ 3 76	
13 70	2 94	16 64	13 28	— 3 36	
15 48	0	15 48	14 35	— 1 13	
15 60	4 31	19 94	21 96	+ 2 04	
16 46	0	16 46	18 33	+ 1 87	
14 88	4 43	19 31	24 86	+ 5 55	
14 90	4 45	19 35	24 39	+ 5 04	
12 59	2 78	15 37	23 09	+ 7 72	27
13 67	3 42	17 09	24 93	+ 7 84	
13 96	0	13 96	21 91	+ 7 95	
14 85	5 46	20 31	16 61	— 3 70	

The nitrogen balance for the whole period is + 69.1 gm. The theoretical value of the nonprotein nitrogen of the blood, calculating from the first observation of 29 mg per 100 c c, should be 119 mg, provided the retained nitrogen were circulating as waste nitrogen, the actual value is 27 mg.

In view of the fact that the above cases were observed over a short time only, and were put on rather a bizarre diet, it is of interest to note what occurs in individuals studied for a longer period, and on what is an ordinary mixed diet. The following two cases (Cases 5 and 6) were given mixed diets containing a fair amount of meat and broth. They ate what food they chose and the nitrogen was calculated from the amount eaten. Foods which might be expected to vary in their nitrogen content, such as broth, potato, meat, etc., were analyzed in isolated

19 Frothingham and Smillie. THE ARCHIVES INT. MED., 1915, xv, 204

samples, and the content of nitrogen in the other articles of diet was estimated according to Atwater and Bryant's<sup>20</sup> food tables. The nitrogen balances in these two instances, therefore, do not possess the accuracy of the first four cases. However, the error is probably not great enough to interfere with the conclusion that a positive nitrogen balance may occur in nephritis under ordinary circumstances without an increase in the nonprotein nitrogen of the blood. Case 5 in twenty-three days retained 69.1 gm of nitrogen, at the termination of this period, the level of the nonprotein nitrogen of the blood was 27 mg per 100 c c, whereas, the theoretical value would have been 119 mg, had the retained nitrogen been circulating as waste nitrogen. Case 6 in seventeen days retained 35.3 gm of nitrogen, which should have given a theoretical value for nonprotein nitrogen of the blood of 117 mg per 100 c c, the actual value being 74 mg, practically duplicating the control figures at the beginning of the observation.

TABLE 9—DATA OF CASE 6

Nitrogen Gm. in 24 Hours					Nonprotein Nitrogen of the Blood Mg per 100 c c
Urine	Feces	Total Output	Intake	Balance	
9.99	1.68	11.67	13.20	+1.53	71
10.48	0.61	11.09	11.21	+0.12	
12.86	1.15	14.31	13.44	-0.87	
9.89	4.72	14.61	23.03	+8.42	
13.76	1.22	14.98	20.43	+5.45	
21.13	1.74	22.87	21.34	-1.53	
15.81	0.81	16.62	20.83	+4.21	
15.79	1.03	17.42	19.71	+2.29	
20.70	1.32	22.02	21.89	-0.13	
18.57	0.45	19.02	21.64	+2.62	
18.89	1.40	20.29	22.53	+2.24	
16.94	2.60	19.54	23.83	+4.29	
18.00	2.77	20.77	20.32	-0.45	80
18.48	2.09	20.57	25.30	+4.73	
18.85	3.01	21.86	22.78	+0.92	
16.71	2.80	19.51	21.92	+2.41	74
17.46	3.67	21.13	20.14	-0.99	

The nitrogen balance for the whole period is +35.3 gm. The theoretical value of the nonprotein nitrogen of the blood, calculating from the first observation of 71 mg per 100 c c should be 117 mg, provided the retained nitrogen were circulating as waste nitrogen, the actual value is 74 mg.

<sup>20</sup> Atwater and Bryant. Bull. 28, revised Ed. U. S. Dept. Agriculture.

## CASE REPORTS

J W (Med No 34006) Male, aged 24 The urine shows a large amount of albumin, a moderate number of hyaline, granular and epithelial cell casts, and varies in specific gravity from 1.011 to 1.023 The systolic blood pressure is 175, diastolic, 115 The heart, arteries and other organs show no abnormalities There was some subcutaneous edema on admission which disappeared shortly and remained absent during the tests The diagnosis is chronic diffuse nephritis

E F (Med No 33757) Male, aged 36 Albumin was discovered in the urine seventeen years ago For five years there has been polyuria and polydipsia, for two years, failing vision There is moderate thickening of all the peripheral arteries The cardiac impulse is forcible in the fifth interspace, 12½ cm to the left of the median line, indicating some hypertrophy of the heart muscle There is no edema, nor are there other signs of myocardial insufficiency The systolic blood pressure varies between 210 and 195 mm of mercury The eye grounds show marked albuminuric retinitis The urine is large in amount, constantly low in specific gravity, contains about 1 gm of albumin per liter, and on microscopic examination yields a few hyaline casts The phenolsulphonephthalein excretion is 22 per cent in two hours The diagnosis is Advanced degree of chronic diffuse nephritis (secondary contracted kidney)

## DISCUSSION

The conception of the retention of nitrogen in nephritis, as understood by the clinician, generally implies two facts First, that a positive nitrogen balance is usually due to kidney insufficiency, second, that the retained nitrogen is present in the body as waste nitrogen and circulates in the blood, in part, at least, as nonprotein nitrogen From the cases described above it becomes evident that one or both of these postulates do not hold true in a great number of instances It is known that in normal individuals on a high protein diet, containing an adequate carbohydrate portion, a large amount of nitrogen may be retained The same retention may take place in individuals suffering with nephritis and may thus be misleading if used as a measure of the ability of the kidney to eliminate nitrogen On the other hand, if it is supposed that the nitrogen is retained because of insufficient kidney action, then, in some cases, as those cited above, there must be a compensatory action on the part of the muscles and other cellular tissues, in storing or assimilating such an excess of nitrogen and not allowing it to appear in the blood as waste nitrogen The solution of this problem involves the whole question of intermediary protein metabolism, and cannot be fully discussed here

## CONCLUSION

A marked positive balance of nitrogen in cases of nephritis on a mixed diet is not necessarily followed by a corresponding increase in the nonprotein nitrogen of the blood Until these phenomena are elucidated, discretion must be exercised in interpreting a normal figure

for nonprotein nitrogen of the blood as indicating that no nitrogen retention has taken place, and in considering a positive nitrogen balance as an absolute indication of the inability of the kidney to excrete this substance

The Johns Hopkins Hospital

## BOOK REVIEW

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DIABETES MELLITUS Designed for the Use of Practitioners of Medicine By Nellis B Foster, M D, Assistant Professor of Medicine, Cornell University Cloth Price, \$3 net Pp 243 Philadelphia J B Lippincott Company, 1915

Dr Foster has added to the large existing literature of diabetes, not a monograph containing new discoveries, but a valuable compilation of existing knowledge for the general practitioner. This it frankly purports to be, and that there is need for such a book in English admits of little question. The value of such a compilation resides wholly in the critical judgment exercised by the author in selecting from the vast material in the field, in the point of view from which he surveys that material, and the clearness and order of its presentation. The compilation by a man who has done no independent work in a field can have no value because such a man possesses no basis for critical judgment.

Dr Foster has been a student of diabetes both from the clinical and the biochemical standpoints, and he has succeeded in selecting what is essential and in presenting with about equal emphasis the important theoretical investigations on which our knowledge of diabetes rests and the practical considerations which determine treatment and prognosis. The book is perhaps best as a sane and simple presentation of the diabetic metabolism. Any clinician who familiarizes himself with the contents of its first eight chapters will have an adequate theoretical basis for his practice. The method of treatment outlined is the orthodox one in vogue for many years, very satisfactorily worked out for the general practitioner with diet tables and reasonably detailed directions. The illustrative cases introduced everywhere make excellent object lessons and add greatly to the usefulness of the chapter on treatment, as well as to that on symptomatology. It is unfortunate for Dr Foster that his book appeared just before the publications of Allen, which have excited so wide an interest in the application of much more rigorous starvation in the treatment of diabetes than has ever previously been attempted. It is well to point out, however, that the exact limitations of the starvation treatment have not yet been clearly determined, and that only a practitioner who has at hand such knowledge as Dr Foster's book presents can wisely apply this newer plan of management.

Such criticisms as can be made concern matters of detail. There are a number of errors due to poor proof reading, and some departures from good usage in the language. An important omission of at least one entire line occurs at the top of page 49. On page 19, in discussing the concentration of the blood in diabetes, it is stated to be unusual, as evidenced by a normal freezing-point, and the "not" seems to have been omitted. In the description of a case of diabetic coma on page 135, the figure for ammonia nitrogen evidently contains a misplaced decimal point. The reviewer would differ with the statement under Symptomatology that rapid wasting is readily explained by the loss of sugar through the urine, for he believes that loss of water is the chief cause of rapid loss of weight. He also believes that fever, rather than a subnormal temperature, is common in coma.

Foster's dicta as to prognosis are based on considerations which seem to the reviewer incontestable in the main, the age of the patient, rather than the severity of the disease existing at the moment, being given the greatest weight. He would, however, feel that the statement that all children succumb within a comparatively short period is too sweeping. Cases of protracted duration of a mild type of diabetes are known to exist in children, and the

reviewer has personal knowledge of them. Such cases were reported, for instance, by Landahl. The explanation of the disappearance of sugar from the urine in older patients with hypertension leaves one without a clear idea of the author's real views. Similarly, in discussing the total metabolism, while giving the views of Benedict, Joslin and others, he does not indicate his own belief. He does, however, quite plainly express his opinion that some of the severest diabetics show the dextrose ratio of 3.65 to 1, on which Lusk has always laid stress. In the treatment of coma by intravenous infusion of alkali, no allusion is made to the use of sodium bicarbonate, made by passing  $\text{CO}_2$  through the solution. Magnus-Levy has shown clearly the value of this. The discussion of the treatment of the surgical complications of diabetes is excellent for so short a book, and the advice given seems very wise, and based on sound clinical observation. The final chapter on the identification of sugars is a useful accompaniment of the book, but it is not very intelligibly presented.

The volume may be recommended to the physician who is not a specialist in the chemical side of medicine as a sane statement of existing knowledge and a sound basis for practice.

#### A CORRECTION

Attention is called to an error on page 7 of THE ARCHIVES for January in the article by Dr Frank A. Evans, "Observations on the Origin and Status of the So-Called 'Transitional' White Blood Cell." The last sentence of the legend of Figure 2 should read "Solid line above, polymorphonuclears, line with crosses, transitionals, line with dots, large mononuclears." The error consisted in a transposition of the descriptions of the lines with crosses and dots, giving an erroneous idea of what the author intended.

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## VENTRICULAR HEMORRHAGE A SYMPTOM-GROUP

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PHILADELPHIA

Hemorrhage in the brain may be extraventricular or intraventricular. In the latter case the blood may originate in the ventricle itself and produce a primary ventricular hemorrhage. In the first, the original seat of the hemorrhage is the tissue surrounding the ventricle and the ventricle itself is only secondarily involved. Secondary effusion of blood into cerebral ventricles is not an infrequent phenomenon, while a primary hemorrhage within the ventricular cavity is rather a rare occurrence, judging from the meager literature on the subject. Not many records are to be found on primary intraventricular hemorrhage. Nevertheless, sufficient data have been accumulated to deserve a special description.

The mechanism of formation, the pathology, the course, the symptomatology of ventricular hemorrhages have been somewhat differently considered by various authors who have had the opportunity to observe such findings. All writers, however, concur in the belief that this form of cerebral hemorrhage is quite infrequent. In view of this infrequency it may be of interest to place on record twelve personal cases of extraventricular and intraventricular hemorrhage studied from anatomical and clinical standpoints. The study of this series suggests a remarkable uniformity in the pathological aspect and in the manifestations during the patients' lives, so that diagnostic inferences appear to be admissible.

Out of the twelve cases seven presented secondary effusion into the ventricles from an original extraventricular area situated close in the vicinity of the cavity. The remaining five cases are examples of primary intraventricular hemorrhage.

I propose to consider first the latter group and the mechanism of formation of the hemorrhage before several other interesting features

### PATHOLOGY

In Cases 2 and 3 sections of the brains were made on the third day of hardening, the blood was washed out thoroughly from the lateral

\* Submitted for publication Nov 12, 1915

~ From the Neuro-Pathological Laboratory of the Mt Sinai Hospital



ventricles and the source of bleeding could be distinctly seen in the choroid plexuses. The choroid plexuses have been considered by many observers as the principal source of intraventricular hemorrhages. From the time of Morgagni, who uniformly considered those plexuses as being the unique source of the bleeding, up to the present time, the majority of observers believe that even in cases in which the seat of the bleeding could not be discovered, the blood vessels of the choroid plexuses are the origin of the ventricular hemorrhage. Degeneration, chronic inflammation, fatty changes, calcareous deposits, dilatation—all these conditions have been observed in the vessels of the plexuses. Thrombosis, aneurisms of the blood-vessels, angiomatous tumors and cysticeri attached to the plexuses have been observed in a few cases (Bioca). Serous cysts originating in the walls of the blood vessels have been found in aged individuals also in cases of atrophy of the brain (Wilks). In the Cases 2 and 3 in which rupture of vessels of the plexus was present, the vessel wall showed fatty degeneration and rounded yellowish masses were seen in the posterior portions of the plexus. These masses were very likely remains of former blood effusions. In all of them pronounced changes were evident in the intima, such as disappearance of the endothelium, degeneration and thickening. The elastica interna usually followed the changes of the intima. The adventitia was found thickened in some vessels, but the media was frequently seen altered, viz., granular and calcareous masses were present. Some vessels were greatly distended with blood, but not to the extent of formation of aneurysm. On none of the sections could a true or false aneurism be detected.

In Cases 1 and 4 after the blood was washed out erosion of the ventricular walls could be seen. Here the blood vessels were found enlarged and distended with blood. Some of them showed calcareous deposits, in others complete occlusion with thrombi was evident. Both individuals were of somewhat advanced age, one 63 years old, the other 67. The ulcerations mentioned were seen on the wall of the corpus striatum in the lateral ventricle.

Case 5 is most interesting from the standpoint of pathogenesis. Nothing abnormal could be found macroscopically, but under the microscope very small aneurysmal enlargements could be seen.

As is well known, miliary aneurysms were considered by Charcot and Bouchard as the chief cause of cerebral hemorrhage. Before them distention of blood vessels and aneurysms were mentioned as causes of cerebral hemorrhage. But since these two observers published their monograph in 1868, the subject of miliary aneurysms was indiscriminately emphasized as being the sole etiologic factor. In their collection of eighty-four cases of cerebral hemorrhage, in all of them multiple

miliary aneurysms were found. In their study they confined themselves to gross pathological changes. They placed the brains in water and small floating masses of tissue with their vascular attachments were picked out and examined under magnifying glasses.



Fig. 1—Primary intraventricular hemorrhage (in lateral cornua on right). Note deviation of the opposite side. Patient operated on.

The subsequent writers on the subject studied miliary aneurysms from the histological standpoint. The intima, the adventitia and the muscularis have all or individually been considered as the origin of aneurysmal dilatation of the blood vessel. Lowenfeld<sup>1</sup> from a study

<sup>1</sup> Lowenfeld. Studien über Aetiologie u. Pathogenese der spontanen Hirnblutungen. Wiesbaden.

of seventeen brains, all with miliaary aneurysms, found in every one the three vessel coats perfectly intact. The weight of opinion of the majority who believe in the existence of miliaary aneurysms, however, is that the changes begin first in the media. The latter degenerates, becomes atrophic, the entire vessel wall becomes then nonresistant, and aneurysmal dilatation follows. This condition occurs especially in the very small cerebral arteries. In a large number of cases no miliaary aneurysms were found and the rupture of the blood vessels was due to a diffuse degeneration of their walls. Kaufman,<sup>2</sup> for example, finds atheromatous changes in the large cerebral blood vessels and hyaline degeneration in the small ones.

Finally, the existence itself of miliaary aneurysms is disputed by some writers.

In my case, after a thorough washing of the hemorrhagic lateral ventricle the brain tissue on the inner wall was seen torn and a number of exposed small vessels could be noticed. Portions of the lacerated tissue were placed in water so as to enable me to observe the blood vessels. Some of them were irregular and projections were seen on their walls. The remainder of the tissue was hardened in Muller's fluid and later examined microscopically. Imbedding was done in celloidin. Staining was done with osmic acid, Weigert's hematoxylin and ammonia carmin. Sections were made longitudinally and perpendicularly to the vessel. Marked changes of the intima and the elastica were found on many sections. Rupture of the intima and blood placed between the latter and elastica were seen on some sections. Swelling of the intima, disappearance of the endothelium, and hyaline appearance of the elastica could also be seen. Lesions of the media were always seen in conjunction with lesions of the intima, degeneration or calcareous deposits, thickening, were observed in the latter. The adventitia was seen split in one or two layers with blood between them. In the aneurysmal dilatations no clear distinction could be made of the individual membranes of the vessel wall. The latter consisted only of a few thin bands infiltrated with leukocytes. The aneurysms were filled with blood and in some sections blood was seen immediately around the vessel. In the latter cases the opening of the ruptured vessel could be traced. A gradual transition from the vessel wall to the aneurysm was noted. In all cases the changes of the intima become more and more marked as the aneurysmal sac is approached. In a number of sections the so-called dissecting variety of aneurysms could be seen, viz., a sacular dilatation of the vessel was present and blood had penetrated between the intima and the media or media and adventitia.

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2 Kaufman. *Specielle Pathologic Anatomie*, 1907.

The histological findings in all the five cases that as far as the mechanism of formation of the lesion is concerned, the latter may be produced by simple rupture of a miliary aneurysm, but in both cases probably all layers of the wall are always present and the hemorrhage is pronounced in the intima



Fig 2—Primary intraventricular hemorrhage (coronary involved) Note deviation of the opposite side

The seat of the primary intraventricular hemorrhage in my five cases, is distributed as follows. Two cases, in one of them blood was found in the lateral ventricle and only in the anterior and posterior horns, in the second case the hemorrhage was confined to one ventricle and only in the posterior cornua. Three cases presented hemorrhage in one lateral

of five cases the right lateral ventricle seems to be the predominant seat of hemorrhage. In only one case was the hemorrhage seen exclusively in the left lateral ventricle.

The seven cases of secondary ventricular hemorrhage present this peculiarity, that here hemorrhage in both lateral ventricles was seen in a larger number (five) than in cases of primary ventricular hemorrhage.

The blood in the ventricles was found coagulated in four cases and fluid in one case. In the latter, death ensued instantaneously. In the former in six, seven, twelve and twenty-four days, respectively. The patient in the latter case was operated on (see below) and at necropsy a firm clot was found. It is interesting to note that in the unilateral cases the ventricle which was free from blood was filled with serous fluid. The walls of the ventricles presented small erosions in three cases. In two cases with diseased blood vessels of the choroid plexuses, the ventricular walls were intact. It is to be presumed that the lacerated face of the ventricles was the result of the diseased vessels and of miliary aneurysms which eventually ruptured. Under the microscope destruction of tissue was seen, but there was no indication of a degenerative state which usually follows softening. The remainder of the brain with its meninges was intact.

In all the five cases the brain tissue in the immediate vicinity of the hemorrhage suffered destruction. In three cases the hemorrhage, besides destroying the surrounding brain tissue and pushing outward the remaining cortical substance, exercised also considerable pressure on the opposite hemisphere and disfigured it. This latter fact, observed at first in one case, suggested a certain surgical procedure for relief of increased intracranial pressure which will be discussed later. In the two other cases the hemorrhage was bilateral so that no marked displacement of brain substance to one or to the other side could be observed.

The pathology of the second series of my cases, seven in number, presents no special features deserving special mention. The original hemorrhage occurred in all in the internal capsule and inundated secondarily the lateral ventricles. Bilateral hemorrhage was present in five out of seven cases. In the two unilateral cases the right lateral ventricle alone was involved. In three cases were found degenerative changes of blood-vessels, especially of the intima, such as was described in the cases of primary ventricular hemorrhage. In four cases multiple miliary aneurysms were seen in the seat of original bleeding. The technic as to preparing the tissue hardening and staining was exactly the same as in the first series.

## DIFFERENTIAL CLINICAL FEATURES

The most interesting manifestations in the primary ventricular hemorrhages of my five cases were the sudden onset, the most profound coma from the very beginning, convulsions more marked on the side opposite to the lesion than on the same side in the unilateral



Fig 3—Primary intraventricular hemorrhage (both lateral ventricles)

cases, and on the side opposite to the seat of the largest hemorrhage in the bilateral cases, finally, absence of marked paralysis—the latter was very slight. These four symptoms were uniformly present in all the five cases at the time when the attack was ushered in

During the comatose state two patients with unilateral hemorrhage had several convulsive seizures, always contralateral, the other three patients had but one initial attack. The most striking phenomenon is the absence of true paralysis. At first similarly to ordinary cerebral hemorrhage, the sudden loss of power was evident, but subsequently during the patient's short life the usual rigidity and contracture did not appear. The absence of rigidity is quite interesting, as since Durand-Fardel, early contracture of the limbs had been considered pathognomonic of primary intraventricular hemorrhage.

Loss of power is very slight. The latter becomes especially evident where the patient attempts in his comatose state to move his limbs or when he defends himself against external stimulations. As to the reflexes, the knee-jerk on the paralyzed side was not especially increased, although it was somewhat greater than on the normal side. Ankle-clonus was absent, the toe phenomenon was also absent. Stimulation of the sole provoked no movement of the toes at all, neither was there any response of the toes with the test for the paradoxical reflex.

In the cases of secondary ventricular hemorrhage the already existing paralysis and contracture became markedly accentuated at the time the ventricles were invaded. The abnormal reflexes which are usually present in hemiplegias were manifest here. All these patients were comatose at the time of the ventricular attack and never regained consciousness during their remaining short life. Among other distinguishing although not constant features of primary ventricular hemorrhage may be mentioned the character of the premonitory symptoms and the duration of the comatose state.

In three of my five patients the attack was ushered in without the least preceding objective or subjective disorder. One patient complained for a few hours of a slight headache, and another patient of a slight vertigo during two preceding days. The attacks consequently bear no relation to the existence or nonexistence of premonitory symptoms. Two of the patients were aged individuals, above 60, and presented evidences of arteriosclerosis, three were of middle age without apparent arterial changes.

The character and duration of the coma are of interest. The latter appeared at the commencement of the seizure, remained complete throughout the short life. In the secondary ventricular hemorrhage the coma was also present with the irruption of the blood into the ventricle. Therefore the mere existence of unconsciousness is of little value in differential diagnosis. It is the sudden onset of profound coma without preceding hemiplegia that will determine the diagnosis of a primary hemorrhage in the ventricle.

In the series of secondary ventricular hemorrhage, death followed but a few hours after the inundation of the ventricle in every case. In the cases of the primary variety, with one exception of instantaneous death, life persisted from six to twenty-four days. The latter patient was operated on, which probably accounts for the longest duration. The subject will be discussed later. The other three patients lived



Fig 4—Primary intraventricular hemorrhage (on right)

though unconscious six, seven and twelve days, respectively. The seat and the size of the hemorrhage have no direct relationship to the duration of life. Thus, in Case 3 the hemorrhage was more extensive than in Case 4. Nevertheless, the former lived twelve days and the latter but six days. On the whole it seems that the fatal issue is less rapid in the primary than in the secondary variety of ventricular hemorrhage.



A rapid glance at the brains in the five cases of primary ventricular hemorrhage shows displacement of the brain tissue to the side opposite the blood in three cases, and consequently the possibility of the comatose state as due to sudden undue pressure on the normal side of the brain appeared to be highly plausible. Such a finding in one case suggested the idea of surgical intervention in other cases with the object of relieving the intracranial pressure on the sound side. Accordingly an attempt was made in one case for a decompressive operation. Although the patient (a woman of 45) did not recover eventually, nevertheless the duration of her life was prolonged to twenty-four days. Immediately after the operation there was a decided improvement in her respiration, in response to external stimulation, in the cardiac action. For several days she could open her eyes voluntarily and when called by her name, she could be fed more readily than before, as she would respond to requests to open her mouth, and she could swallow. On the twentieth day the coma returned and on the twenty-fourth day she expired. The improvement obtained was undoubtedly due to the relief of the intracranial pressure. Unfortunately the operation was consented to only on the fifth day after the apoplectic seizure, viz., after five days of a comatose state. Efforts were made to operate in the other four cases, but permission could not be obtained.

#### SUMMARY

The present study suggests the following interesting features in primary intraventricular hemorrhage

- 1 From a diagnostic standpoint sudden onset without premonitory symptoms, profound coma at the outset and continuing for several days without improvement, absence of genuine paralysis, absence of rigidity and contracture during the days following the seizure, absence of the toe phenomenon—all of these manifestations speak in favor of primary ventricular hemorrhage.

It should be borne in mind that in all the five cases the hemorrhage occurred only in the lateral ventricles. The above mentioned phenomena were observed in but five cases. The number is too small to draw general conclusions. Nevertheless they appeared sufficiently uniform to permit the possibility of their pathognomonic nature, at least in cases when hemorrhage occurs in the lateral ventricles alone.

- 2 The next important feature of the subject is the surgical intervention on the sound side based on the existence of a displacement of the brain to that side. It is possible that the profound comatose state is due precisely to the sudden compression of the normal brain tissue. The amount of improvement obtained in one case was a sufficient encouragement in that direction. If a decompressive operation on the

sound side is to be undertaken, it must be done promptly after the onset. In my case the operation was performed on the fifth day and in spite of this delay some amelioration of the condition was decidedly



Fig 5—Primary intraventricular hemorrhage (both lateral ventricles)

manifest. It is to be presumed that the earlier relief from intracranial pressure is obtained, the more prolonged the favorable results that will be observed.

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# THE GASTRIC MUCOSA IN DELIRIUM TREMENS

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In the experience of Dr. E. R. Le Count, coroner's physician in Chicago, petechial hemorrhages in the stomach lining are among the most constant lesions found in the bodies of persons dying during the acute delirium of chronic alcoholism. This condition has been considered an acute alcoholic gastritis, but in the absence of any microscopic examination of similar lesions, the nature of these changes was called in question. The present study, therefore, was taken up with the view of determining the microscopic appearance of these hemorrhages, and to see if they actually are a part of an acute inflammation.

Kayser<sup>1</sup> in a report of the gross anatomic changes in the bodies of 120 persons dying with delirium tremens, mentions thirteen instances of hyperemia or ecchymoses in the sixty-nine bodies in which changes in the stomach were noted. An inquiry into the literature for microscopic studies on the stomach in chronic alcoholism disclosed only a few such investigations, with very little comment on the condition of the organ in delirium tremens. On the whole, the stomach condition, where it has been mentioned, is dismissed with the gross descriptive term of "chronic gastritis," without further inquiry into the character of the microscopic picture. In all of the reported examinations of the stomach in chronic alcoholism there is no record of hemorrhages in the gastric mucosa. The omission of a microscopic examination of the gastric mucosa is not surprising when the difficulties of obtaining freshly fixed material are appreciated, and unless the stomach tissue is removed almost immediately after death, autodigestion occurs so rapidly as to make useless an histological study.

In the experimental studies on the influence of alcohol on lower animals some interesting changes have been noted in the stomach. Kremiansky,<sup>2</sup> working with dogs, observed a slight catarrhal inflammation of the stomach and bowel, manifested by an edema, thickening, and

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<sup>1</sup> Submitted for publication, Nov. 9, 1915.

<sup>\*</sup> From the Laboratories of Pathology of Rush Medical College and the University of Chicago.

1 Kayser, O. *Ein Beitrag zur Alkoholfrage*, I D., Kiel, 1888.

2 Kremiansky, J. *Ueber die Pachymeningitis interna hemorrhagica bei Menschen und Hunden*, *Virchows Arch. f. path. Anat.*, 1868, xlii, 321.

slight pigmentation Ruge,<sup>3</sup> after introducing alcohol into the stomachs of dogs through a tube, found hyperemia of the mucosa in some, ecchymoses in one, blood-stained feces in another, and marked swelling of the gastric mucosa in a third. No changes were seen in the tissues of rabbits receiving alcohol subcutaneously from four to thirteen days. During an experimental study of alcoholic liver cirrhosis in rabbits, Straus and Blocq<sup>4</sup> found changes to a greater or less degree in all stomachs. In the stomachs of those animals dying within the first days or weeks there were erosions and hemorrhages, of those surviving a longer period of experimentation there were either healed or nearly healed ulcers. The mucosa of the latter was pale, thickened, and generally covered with mucus. Naturally, as Quensel<sup>5</sup> suggests, the mechanical effect of the stomach tube in these experiments must be considered. Microscopically, the gastric mucosa of these animals was infiltrated with round cells. Dujardin-Beaumetz and Audige<sup>6</sup> observed hyperemia of the alimentary tract with occasional hemorrhages. Afanassijew,<sup>7</sup> after introducing alcohol into the stomachs of dogs, rabbits, guinea-pigs, and rats, found a marked increase of the mucous secretion, and a considerable hyperemia of the mucosa. Occasionally extravasations of blood were present in the mucosa of dogs' stomachs, lesions rarely seen in the stomachs of rabbits. Microscopically these hemorrhages in the gastric mucosa were of variable size, sometimes extending through the entire width of the mucosa, and covering a considerable surface area. From a very limited experimental series (two dogs), Chretien<sup>8</sup> concludes that alcohol produces in the dog a chronic gastritis with the formation of cysts and a return of the mucosa to an embryonic state. These changes, he says, correspond with those described under the name "mucous gastritis." Braun,<sup>9</sup> feeding rabbits and dogs with alcohol for a considerable period of time, could not confirm the changes described by Afanassijew. In several rabbits he observed stomach erosions and recent hemorrhages, which he thinks

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3 Ruge, P. Wirkung des Alcohols auf den thierischen Organismus, *Virchows Arch f path Anat*, 1870, xlix, 252

4 Straus and Blocq. Etude experimentale sur la Cirrhose alcoolique du Foie, *Arch de Phys norm et path* 1887, x, 409

5 Quensel, Ulrik. Alkoholfragan fran Medicinsk Synpunkt. Uppsala and Stockholm, 1913

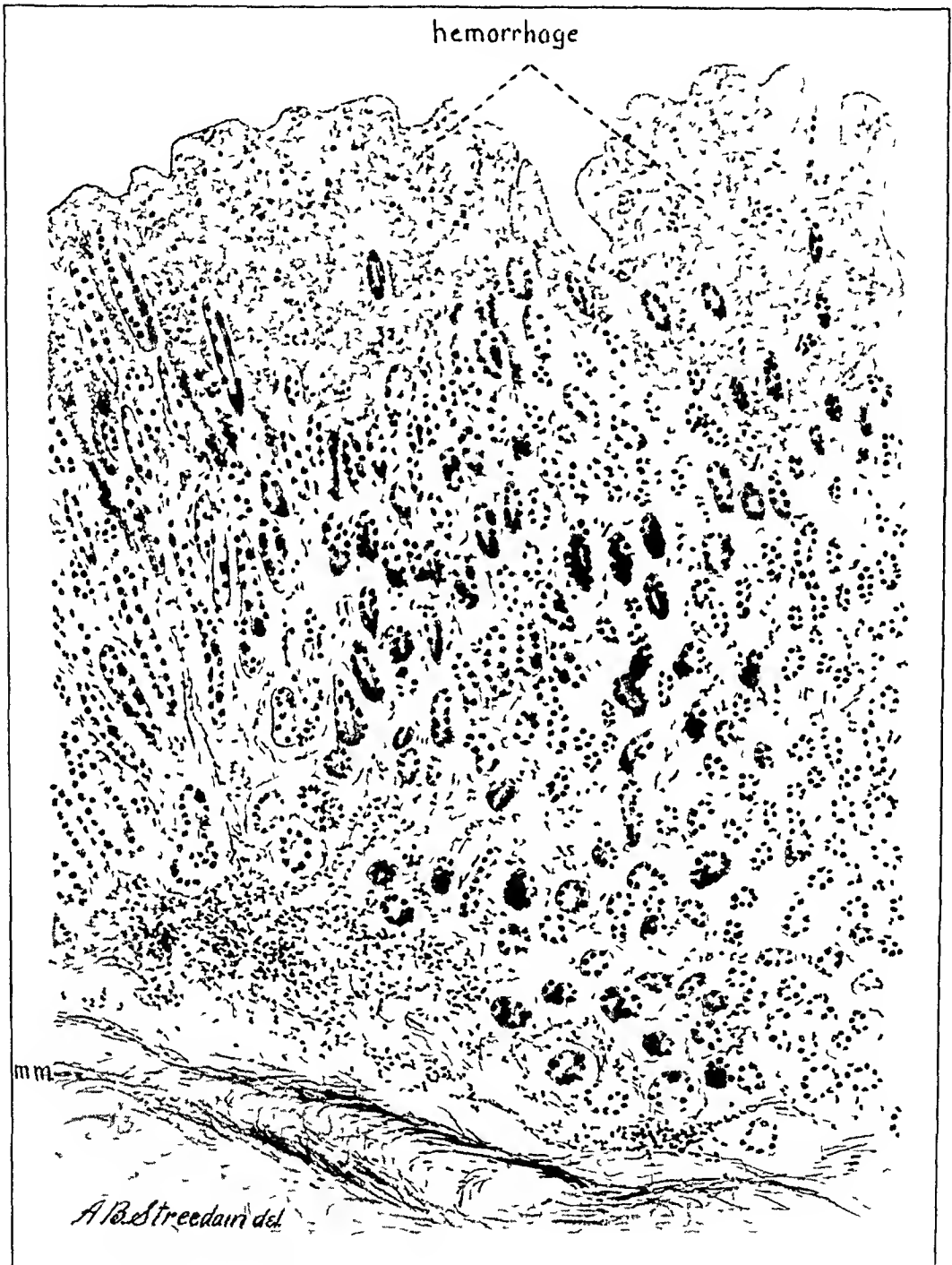
6 Dujardin-Beaumetz and Audige. Recherches expérimentales sur l'alcoolisme chronique, *Compt rend de l'Acad d Sc*, 1883, xcvi, 1557

7 Afanassijew, W. A. Zur Pathologie des acuten und chronischen Alkoholismus, *Ziegler's Beitr*, 1891, ix, 349

8 Chretien, M. Sur les Altérations de la Muqueuse gastrique et les modifications du Chimisme sous l'influence de l'ingestion prolongée d'Alcool. These Lille, 1897

9 Braun, H. Ueber die experimentelle durch chronische Alkoholintoxication hervorgerufenen Veränderungen in zentralen und peripheren Nervensystem. Inaugural Dissert., Tübingen, 1899

resulted from the alcohol, this having been given in rather high concentrations. Baumgarten<sup>10</sup> gave alcohol to rabbits by mouth and subcutaneously. With both methods of administration he observed



Low power sketch locating the hemorrhages in the gastric mucosa, and illustrating the absence of acute inflammation about them

10 Von Baumgarten Ueber die durch Alkohol hervorgerufenen pathologisch-histologischen Veränderungen, Verhandl d Deutsch Path Gesellsch, 1907, 21, 229

numerous hemorrhagic erosions of the gastric mucosa. Since the mechanical factor is absent in animals receiving alcohol subcutaneously, Baumgarten believes that the stomach lesions are not produced mechanically, but that they have some relation to the alcohol action, probably being the result of some vascular disturbance, such as a vasomotor spasm producing an anemic necrosis on which the gastric secretions act. D'Amato<sup>11</sup> observed in the stomachs of two dogs daily receiving alcohol over a period of three and a half months, hyperemia, parenchymatous and interstitial inflammation. Fahr,<sup>12</sup> experimenting with guinea-pigs and rabbits for long periods, observed no changes in the stomachs of the guinea-pigs, but in those of the rabbits he noted a distinct reddening. Microscopically there was nothing abnormal.

From this brief review, in which no attempt is made to collect all the experimental data concerning the effect of alcohol on the stomach of animals, there is noted a considerable divergence of observed conditions. Quensel does not think a clear and definite picture of the effect of alcohol on the stomach wall is possible from these studies. As is well known, alcohol in strong concentrations acts as a caustic on the gastric mucosa, and inasmuch as some experimenters gave alcohol in this form, an explanation for their findings seems probable. However, such strong alcohol is rarely used by chronic alcoholics.

To obtain material satisfactory for microscopic study, Zenker's fixing fluid was introduced into the stomach by means of a stomach tube immediately after death. During the postmortem examination later, portions of the fixed stomach were removed and preserved in alcohol. Of the twenty-one stomachs examined in this way, nine are from bodies that anatomically confirmed the clinically diagnosed delirium tremens, the other twelve stomachs are from the bodies of persons dying from various other disorders, some having been chronic alcoholics for many years. The latter group serves as a comparative control in this study. For the microscopic study, small pieces of tissue from both the anterior and posterior walls, respectively, in the pyloric, fundic, and cardiac regions of each stomach, were embedded in paraffin, sectioned, and stained with hematoxylin and eosin in the usual way. Thus large series of sections were prepared with tissues taken from six different regions of each stomach, making possible a careful examination.

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11 D'Amato, L. Ueber experimentelle vom Magendarmkanal aus hervorgerufenen Veränderungen der Leber und über die dabei gefundenen Veränderungen der übrigen Bauchorgane, *Virchows Arch f path Anat*, 1907, cxvii, 435.

12 Fahr. Beiträge zur Frage des Chronischen Alkoholismus. *Virchows Arch f path Anat*, 1911, ccv, 397.

Table 1 contains the histological report of the delirium tremens stomach with a brief statement of the cause of death, and some clinical and anatomic notes of interest. Table 2 contains similar data for the stomachs studied as controls.

The mucosa of all the stomachs removed from persons dying with delirium tremens contains hemorrhages of varying dimensions. The largest are easily recognized with the unaided eye, while the smallest are microscopic in size. All of these hemorrhages lie in that portion of the mucosa immediately adjacent to the stomach lumen, and none is found in the deeper portion, nor in the submucous or muscular layers. Microscopically, the smallest hemorrhages are minute areas of tissue edema with a small number of red blood corpuscles lying free in the interstitial tissue spaces. The larger ones are extensive collections of red blood cells closely packed into the tissues of the mucosa. There are no polymorphonuclear leukocytes either among the red corpuscles in these hemorrhages or in the surrounding tissues. In fact, the absence of changes indicating acute or chronic inflammatory processes is striking. Only a few widely isolated, small collections of polymorphonuclear leukocytes in and about some of the stomach tubules have been observed, and these without exception have had no relation with the hemorrhages described.

There are no hemorrhages in the mucosa of the stomachs used in this study as comparative controls, except those in which death was accompanied by or resulted from an acute toxic condition.

Excepting for the presence of hemorrhages, the stomach in delirium tremens is unaltered to any great extent. This is of especial interest, inasmuch as chronic alcoholism frequently is said to produce a chronic catarrhal gastritis. In only three of the twenty-two stomachs examined is there any microscopic evidence of a mucoid degeneration of the epithelium, and comparison with tissues used by Bensley<sup>13</sup> in describing the normal histology of the stomach revealed no striking alteration excepting as mentioned.

The occurrence of petechial hemorrhages in the gastric mucosa of persons dying in delirium tremens affords additional evidence on which a gross anatomic diagnosis of this disorder may be made. In the absence of acute toxic processes accompanying death, the presence of multiple petechial hemorrhages in the stomach lining is of great significance, and when taken into account with the clinical and other anatomic data, affords a substantial basis for ascribing the cause of death to delirium tremens. Kayser's report of anatomic changes in delirium tremens is simply a tabulation of changes present in the bodies

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13 Bensley, R. R. *Ref. Handb. Med. Sc.*, 1904, (7), 461.

TABLE 1—DATA CONCERNING DELIRIUM TREMENS STOMACHS

No	Microscopic Study of Gastric Mucosa	Cause of Death	Clinical and Anatomic Notes
1	Large hemorrhages in the fundus and cardia	Delirium tremens	Aged 30 Came to the hospital irrational, became wildly irrational and died shortly after
2	Small hemorrhages in the fundus and cardia Moderate atrophic gastritis	Delirium tremens	Aged 50 Observed one day Anatomically, delirium tremens
3	Very small hemorrhages, marked hyperemia, small collections of polymorphonuclear leukocytes in and about the tubules, moderate atrophic gastritis	Delirium tremens	Aged 52 Observed one day with diagnosis of chronic alcoholism Had been a chronic alcoholic for 30 years
4	Numerous small hemorrhages, marked hyperemia, moderate post-mortem changes	Delirium tremens	Aged 29 Observed four days Was an habitual heavy drinker, irrational when admitted, present bout of a week's duration
5	Few small hemorrhages, moderate hyperemia, slight post-mortem changes	Delirium tremens	Aged 38 Observed two days Was irrational when admitted, had been a chronic alcoholic for twenty-three years
6	Numerous small hemorrhages, marked hyperemia and edema small collections of polymorphonuclear leukocytes in and about some of the tubules	Delirium tremens	Aged 44 Observed one day without a clinical diagnosis Anatomically only delirium tremens
7	Widely disseminated small hemorrhages, small areas of mucoid degeneration of the tubular epithelium, and small collections of polymorphonuclear leukocytes about some of the tubules	Delirium tremens	Aged 44 Was a heavy drinker for twenty-four years Clinically diagnosed delirium tremens Anatomically had disappearing contusions of the cerebral cortex
8	Numerous small, widely disseminated hemorrhages, moderate hyperemia	Delirium tremens	Aged 50 Had been drinking indefinitely when arrested, observed eighteen days, on the second became irrational, and later developed pneumonia Anatomically pseudolobar bronchopneumonia
9	Very small hemorrhages, mucoid degeneration of the glandular epithelium	Delirium tremens	Aged 47 Observed five days with clinically diagnosed delirium tremens and chronic nephritis



TABLE 2—CONTROL STOMACHS

No	Microscopic Study of Gastric Mucosa	Cause of Death	Clinical and Anatomic Notes
1	Small hemorrhages in the fundus and cardia, moderate atrophic gastritis	Meningitis	Aged 40 Observed two days, irrational when admitted, skull fracture suspected Anatomically, suppurative otitis media and lateral sinusitis
2	Moderate edema, marked atrophic gastritis	Skull fracture	Aged 83 Was irrational when admitted and clinically diagnosed delirium tremens
3	Moderate hyperemia and edema, slight atrophic gastritis	Spontaneous hemorrhage	Aged 50 Pachymeningitis hemorrhagica Clinically diagnosed delirium tremens and lobar pneumonia Anatomically marked compression of the brain, but no skull fracture found
4	Slight edema and hyperemia	Fractured calcaneus (Fat embolism?)	Aged 39 Observed one day, four days before entry fell from a ladder, drank periodically ten to fifteen glasses of whiskey daily
5	Small hemorrhages in the cardia	Pulmonary and generalized miliary tuberculosis	Aged 42 Observed one day
6	Slight edema and hyperemia	Lobar pneumonia	Aged 22 Lobar pneumonia clinically and anatomically
7	Moderate hyperemia and edema, marked postmortem changes	Perirectal abscess, pneumonia	Aged 38 Observed twelve days with clinically diagnosed delirium tremens and lobar pneumonia Anatomically, burrowing perirectal abscess, pyemia and pneumonia
8	Moderate hyperemia and edema, slight mucoid degeneration and atrophy of the gastric glands	Lobar pneumonia	Aged 40 Clinically and anatomically lobar pneumonia
9	Moderate hyperemia, small collections of polymorphonuclear leukocytes about some of the tubules, moderate atrophic gastritis	Skull fracture	Aged 50 Observed thirty minutes Had been drinking for three days and on the day before entering the hospital a friend had noticed him acting queerly
10	Numerous hemorrhages	Tuberculous meningitis and peritonitis	Aged 38 Observed six days, history of being an habitual drinker
11	Slight hyperemia and edema	Lobar pneumonia	Aged 28 Observed three days under the clinical diagnosis of chronic alcoholism and lobar pneumonia
12	Slight hyperemia and edema	Spontaneous (?) subdural hemorrhage	Aged 34 Admitted unconscious and observed one day Stated he had been struck on the head two days previously, had been drinking A large subdural blood clot was removed during an operation

of persons clinically diagnosed as having delirium tremens. This tabulation does not take into account delirium in every way resembling that produced by alcohol, but due to some other entirely different factor, such as meningeal hemorrhage, lobar pneumonia, tuberculous meningitis, skull fracture with sinus thrombosis and acute meningitis, suppurative meningitis, cerebral hemorrhage, trichinosis, bone fractures, icterus, suppurative cystitis and prostatitis, and acute tuberculous peritonitis. These conditions certainly could produce a delirium in every respect resembling that of delirium tremens. The elimination of such doubtful instances of delirium tremens would diminish considerably the number of necropsies reported by Kayser, and would increase materially the percentage of instances in which petechial hemorrhages occurred in the gastric mucosa.

That simply the chronic alcoholism produces the petechial hemorrhages in the stomach lining is not borne out by the repeated examination of the stomachs of chronic alcoholics when such changes are not present in the mucosa. Quensel<sup>5</sup> records an autopsy on a chronic alcoholic, a carpenter by trade, who had used intoxicating liquors in large quantities for a long time. In the stomach, Quensel found a large piece of resin, an indigestible substance contained in an alcoholic solution which the man used in his trade, and which he from time to time had taken as a beverage. Microscopically, only slight changes consisting of some increase in the interstitial tissue were noted. This observation agrees well with the changes noted in the present study where only glandular atrophy and corresponding interstitial tissue changes occurred, these not uniformly present and not necessarily the effect of a chronic alcoholism.

The presence of petechial hemorrhages in the stomach lining of persons dying in delirium tremens affords additional evidence that there is some acute toxic process in this disorder other than the simple alcohol poisoning. In a previous communication<sup>13</sup> this idea was expressed, and while at present the exact nature of this toxic condition remains unknown, it is hoped that further studies will ultimately reveal the basic factors acting in acute alcoholic delirium.

#### SUMMARY

1 Petechial hemorrhages in the gastric mucosa are among the most common lesions present in the bodies of persons dying in delirium tremens.

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13 Hirsch, Edwin F. A Morphologic and Chemical Study of the Double Refractive Fats of the Adrenals in Delirium Tremens, Jour. Am. Med. Assn., 1914, LXIII, 2186.

2 There is no evidence of any acute inflammation about these hemorrhages, thus leaving no anatomic basis for considering this condition in the stomach an acute alcoholic gastritis

3 These hemorrhages probably are anatomic manifestations of an acute toxemia

4 Chronic alcoholism alone is of doubtful etiologic importance in causing chronic gastritis

My sincere thanks are here expressed to Drs E R Le Count, H G Wells, and C Scelesh for their kind assistance



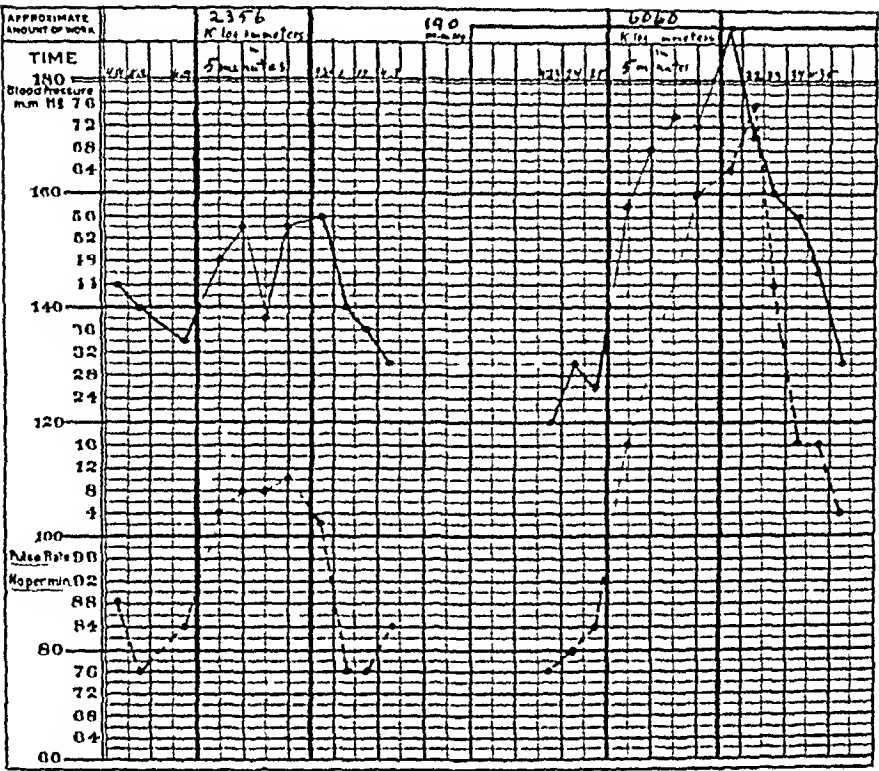


Chart 1—Circulatory reactions in a normal man to increasing amounts of work performed on the bicycle ergometer. The upper continuous lines represent the systolic blood pressure, the lower dotted lines the pulse rate and the spaces between the heavy perpendicular lines the periods of work in each experiment.

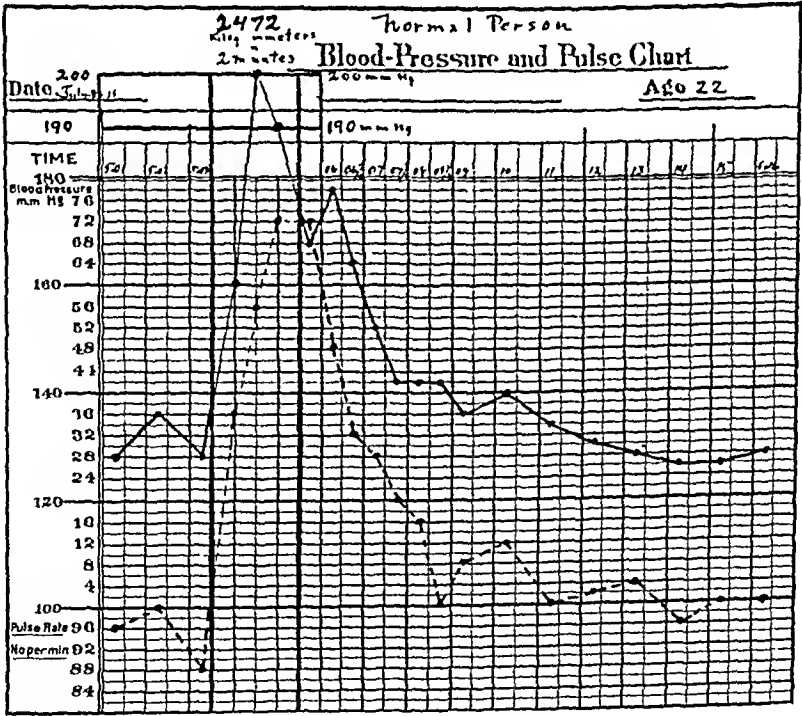


Chart 2—See Chart 1

was panting and perspiration was running from his face. Immediately after the work stopped the systolic pressure was 168, and one minute later had risen to 178 at which time the pulse had dropped from 172 to 148. This delayed rise of the systolic blood pressure after heavy work is of much significance and we direct particular attention to it.

Experiments were carried out on two other people with normal hearts with the same results as above, an increase in pulse rate and blood pressure during work and a delayed rise of the systolic pressure following very heavy work.

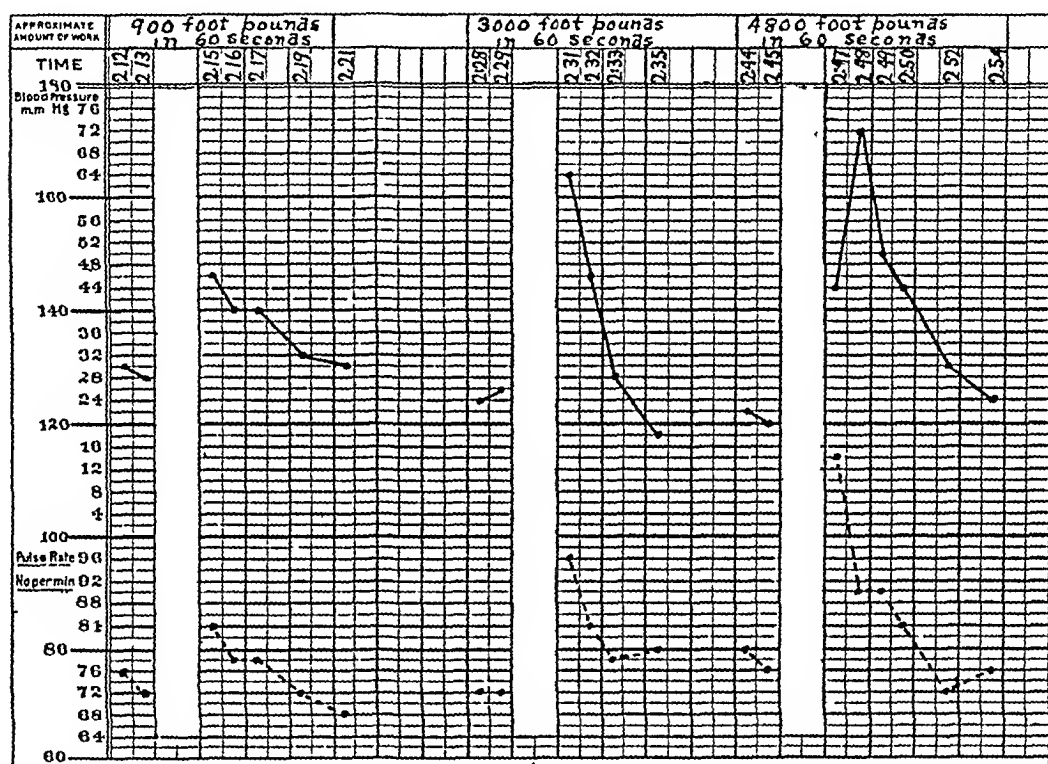


Chart 3—Circulatory reactions in a normal man to increasing amounts of work performed by means of dumb-bells. The white perpendicular spaces represent the work periods in each experiment during which blood pressure and pulse rate could not be measured.

#### EXPERIMENTS ON NORMAL PEOPLE WITH DUMB-BELL AND BAR WORK

Various movements with heavy dumb-bells and a steel bar weighing 25 pounds, which will be described later, were carried out in a way which permitted an approximate estimation of the foot-pounds of work performed. Naturally the pulse rate and blood pressure could not be taken during the work, but they were taken before and every minute or half minute after work.

Chart 3 represents the type of reaction we obtained in several hundred experiments on twenty normal persons. The delayed rise in systolic blood pressure was obtained after large amounts of work which varied according to the subject's physique and condition of muscular training.

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THE ARCHIVES OF INTERNAL MEDICINE

EXPERIMENTS ON PATIENTS WITH CARDIAC INSUFFICIENCY USING THE ERGOMETER

Ten experiments were carried out on two patients who rode the bicycle ergometer for periods of two and one-half minutes with successively increasing loads. Seven experiments were made with the same patients turning the bicycle pedals by hand instead of by the feet. This was done to see if approximately the same amount of work would be followed by a delayed rise in systolic pressure, whether performed by the legs or the arms.

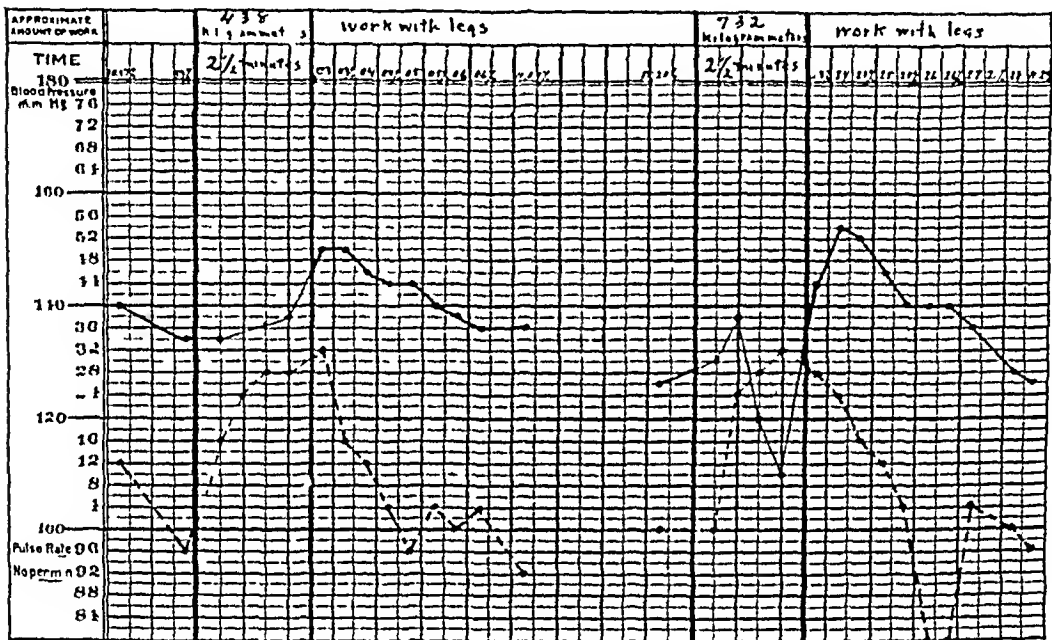
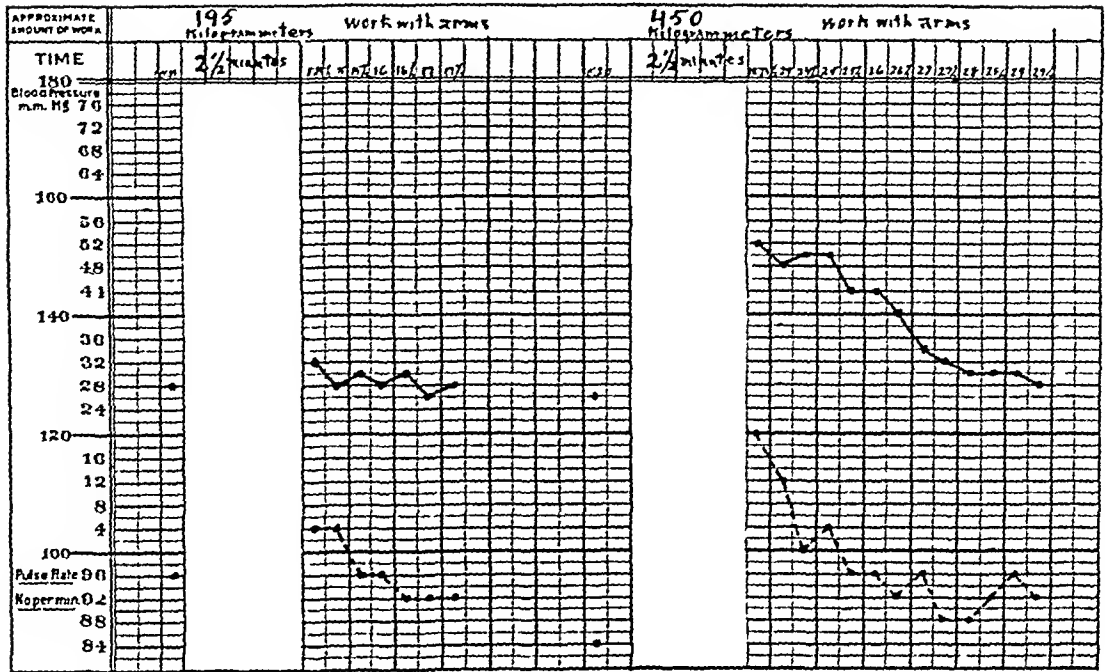


Chart 4—Circulatory reactions in patient C G suffering from cardiac insufficiency to increasing amounts of work performed with the legs on the bicycle ergometer

Charts 4, 5, and 6 show a typical group of experiments on one of these patients, suffering from mitral regurgitation and cardiac insufficiency. The blood pressure could not of course be measured during the arm work. It will be noticed that 732 kilogrammeters performed with the legs is followed by a marked delayed rise, and 729 kilogrammeters performed with the arms shows an equally marked delay.

The subjects of these experiments both had badly damaged hearts, and histories of two or more attacks of cardiac insufficiency extending over several years.

These experiments present several striking features and some marked contrasts to the experiments on normal persons. The amounts of work necessary to produce the delayed rise in systolic blood pressure were far less than in the normal subjects. Again the pressure *during* work, instead of rising decidedly as in normal subjects, rose but slightly or fell below the pre-exercise level.





EXPERIMENTS ON PATIENTS WITH CARDIAC INSUFFICIENCY USING  
DUMB-BELL WORK

Several hundred experiments were carried out on thirty different patients. The pulse rate and blood pressure could not be taken during the performance of the dumb-bell work, but were measured every thirty or sixty seconds after work.

The following examples are selected because they represent the different types of reactions following work.

R S, a delicate girl aged 23, with a history of chorea and tonsillitis followed by endocarditis. This resulted in a mitral stenosis and regurgitation and, five months previous to the test below described, cardiac decompensation from which she slowly recovered under rest and digitalis.

Time	Pulse Rate	Systolic Blood Pressure
10 05	92	108
10 08	96	104
200 foot-pounds in 30 seconds (5 lb bell pushed 20 times)		
10 10	114	122
10 10½	108	120
10 11½	92	106
10 16	90	106
400 foot-pounds in 30 seconds (10 lb bell pushed 20 times)		
10 18	120	110
10 18½	108	110
10 19½	98	106
10 30	96	110
480 foot-pounds in 32 seconds (10 lb bell pushed 24 times)		
10 31	120	114
10 32	102	Delayed rise 122
10 33	90	110
10 34	90	110

C G, a man aged 31, with a history of four attacks of rheumatic fever, and symptoms of cardiac involvement for four years. June 8, 1915, he was recovering from a six months' attack of acute articular rheumatism. His heart was much enlarged and showed a mitral regurgitation and regular rhythm. He was dyspneic, his legs were edematous, and the edge of the liver could be felt 5 inches below the free border of the ribs in the nipple line. He was put to bed and given digitalis. June 21, the following test was made.

Time	Pulse Rate	Systolic Blood Pressure
10 55	100	136
10 58	88	130
11 00	100	126
250 foot-pounds in 20 seconds (10 lb bell flexed 10 times)		
11 02	108	138
03	108	136
04	96	132
05	92	126
06	90	128
11 22	96	128

500 foot-pounds in 35 seconds  
(10 lb bell flexed 20 times)

11 23½	106	140
11 24	102	130
11 25	96	136
11 26	92	130
11 28	100	128
11 34½	96	122

750 foot-pounds in 45 seconds  
(10 lb bell flexed 30 times)

11 37	114	146
11 38	102	136
11 39	102	136
11 42	96	136
11 44	100	122

1,000 foot-pounds in 40 seconds  
(15 lb bell flexed 27 times)

11 47	126	Delayed rise {	136
11 48	114		142
11 49	108		138
11 50	108		134
11 51	96		138
11 52	96		124

These show the ordinary types of reaction to increasing work

The same patient several months later showed a type of reaction occasionally encountered

Time	Pulse Rate	Systolic Blood Pressure
10 05	92	124

462 foot-pounds in 35 seconds  
(15 lb bell flexed 15 times)

10 07	102	140
10 07½		134
10 08	100	134
10 15	92	126

750 foot-pounds in 35 seconds  
(20 lb bell flexed 15 times)

10 17	108	140
10 17½		136
10 18	84	126
10 20	88	132

1,000 foot-pounds in 45 seconds  
(20 lb bell flexed 20 times)

10 22	108	134
10 22½	96	130
10 23		128
10 23½	90	128
10 29	92	122

1,250 foot-pounds in 60 seconds  
(20 lb bell flexed 25 times)

10 31	108	Delayed rise ? {	126
10 31½	102		128
10 32	90		126
10 39	92		126

1,500 foot-pounds in 60 seconds  
(20 lb bell flexed 30 times)

10 43	114	Delayed rise	{ 124
10 43½			{ 126
10 44	92		{ 124
10 44½	90		{ 128
10 45	84		{ 120
10 46	84		{ 124
10 47	84		122

The blood pressure reactions to work became less and less marked as the work increased, although the pulse became more and more rapid. Finally in the fourth experiment we got apparently a slight delayed rise in systolic pressure, and, when the work was still more increased (fifth experiment) the pressure immediately after work was lower than it was before, although the pulse-rate had risen to 114.

One more example of the last type may be given.

D. C., aged 23, suffering from disease of all the valves except the pulmonary, and cardiac insufficiency, died Jan 1, 1915. December 9 he showed the following

Time	Pulse Rate	Systolic Blood Pressure
12 25	84	100

150 foot-pounds in 20 seconds

12 26	108	102
27	96	102
28	90	102
30	80	100
12 40	84	98

200 foot-pounds in 20 seconds

12 41	104	Delayed rise	{ 100
42	96		{ 108
43	88		{ 106
48	90		{ 102
1 05	84		106

350 foot-pounds in 25 seconds

1 06	108	Delayed rise	{ 98
07	102		{ 106
08	96		{ 110
09	90		{ 110
13	90		100

#### EXPERIMENTS DEMONSTRATING THAT THE AMOUNT OF WORK NECESSARY TO PRODUCE A DELAYED RISE IN SYSTOLIC BLOOD PRESSURE IS THE SAME WHATEVER GROUP OF MUSCLES IS EMPLOYED

This is the first time as far as we can ascertain that this law of 'circulatory' physiology has been demonstrated. Proof of the invariability of this phenomenon was afforded, as previously stated, by three experiments on two patients with cardiac insufficiency, using the ergometer, and also by many other clinical experiments. A few of the latter will be given for this law plays an important part in establishing the validity of our test of the heart's functional capacity.

The patient on whom the following experiments were performed was aged 58 years had a normal heart and suffered from occasional attacks of moderate hypertension. On each of the five days preceding the experiments described below this patient had been able to do between 1,500 and 1,800 foot-pounds of work before delayed rises were produced.

Time	Pulse Rate	Systolic Blood Pressure
10 45	96	146
1,500 foot-pounds (approximate) in 35 seconds (Work performed with right arm by swinging 20 lb bell 8 times)		
10 47	108	164
48	100	160
49	96	152
50	92	148
1,800 foot-pounds (approximate) in 40 seconds (Work performed with right arm by swinging 20 lb bell 10 times)		
11 17	114	{ 154 158 156 154 140
18	96	
19	90	
20	90	
24	84	140
1,800 foot-pounds (approximate) in 40 seconds (Work performed with left arm by swinging 20 lb bell 10 times)		
11 26	120	{ 156 170 156 150 148 140 140 140
27	96	
28	96	
29	90	
30	90	148
32	84	140
11 40	9	140
11 45	92	140
1,800 foot-pounds (approximate) in 40 seconds (Work performed with both arms by swinging two 10 lb bells 10 times)		
11 47	108	{ 154 164 150 150 142 138 136
48	96	
49	90	
50	90	
51	84	142
52	80	138
11 53	84	136

It will be seen that it makes no difference whether one or both arms are used to do the work, as far as concerns the production of the delayed rise.

E B, a patient aged 40 years suffering from mitral regurgitation and stenosis and moderate cardiac insufficiency showed the following results.

Time	Pulse Rate	Systolic Blood Pressure
11 28	96	120
400 foot-pounds (12 lb. bell extended 20 times)		
11 29	120	128
29½	112	126
30	108	120
30½	108	116
31½	104	116
33	100	116

500 foot-pounds (12 lb bell extended 25 times)			
11	34	124	Delayed rise {
	34½	120	
	35	116	
	35½	104	
	36½	108	
	50	104	
396 foot-pounds (12 lb bell flexed 18 times)			
11	51	136	138
	51½	112	130
	52	104	128
	52½	108	122
	53	100	122
	58	104	116
440 foot-pounds (12 lb bell flexed 20 times)			
11	59	140	Delayed rise {
	59½		
12	00	108	
	00½	108	
	01	108	
	02	104	

Five hundred foot-pounds of extensor work and 440 foot-pounds of flexor work produced a delayed rise of blood pressure

As a general rule to which the above experiment is an exception a patient with mitral disease is able to do more flexor work with the arms than extensor work, before a delayed rise is produced. Extensor work apparently produces an obstacle to the pulmonary circulation because it tends to immobilize the thorax, while flexor work does not do so. Graupner first called attention to this.

#### SUMMARY

Our work may be summarized as follows

*Experiments on Three Normal Persons with Ergometer*—During increased amounts of work there was a rise of the systolic blood pressure and an increase of the pulse rate which became very marked with heavy work. After heavy work the delayed rise in systolic blood pressure was noted.

*Experiments on Normal People with Dumb-Bell Work*—Several hundred experiments on twenty normal people showed the delayed rise in systolic pressure after heavy work.

*Experiments on Two Patients with Cardiac Insufficiency Using the Ergometer*—Ten experiments showed a marked contrast in the course of the blood pressure during work as compared with that in normal persons. In these patients the pressure rose but slightly and as the work increased frequently dropped below the original level. The pulse rate was always quickened. The delayed rise in systolic blood pressure occurred after much smaller amounts of work than in normal persons. Approximately the same amounts of work were followed by a delayed rise whether performed by the arms or legs.

*Experiments on Patients with Cardiac Insufficiency Using Dumb-Bell Work*—Several hundred experiments were carried out on thirty patients. The delayed rise in systolic blood pressure was noted in all these patients after comparatively small amounts of work. In patients with marked cardiac insufficiency the pressure immediately after work was occasionally lower than the original level.

#### THE CIRCULATORY PHYSIOLOGY OF EXERCISE

Certain facts about the circulatory physiology of exercise seem to be fairly well established, and we shall summarize them briefly.<sup>2</sup> The carbon dioxide content of the blood is increased by muscular work and this stimulates the nervous centers controlling the suprarenal glands. An increase in the adrenin content of the blood is thereby produced, which causes a constriction of vessels in the splanchnic area and a resulting rise in blood pressure. The quickened heart rate accompanying muscular work causes an increase in the quantity of blood discharged by the heart per minute and this also contributes to the rise in blood pressure. Shortly after exercise stops, the carbon dioxide content of the blood falls below normal, the activity of the suprarenal glands decreases and the splanchnic vessels relax.

Nicolai and Zuntz<sup>3</sup> have made some important observations on the hearts of a series of normal persons during work on a stationary ergometer by means of the Roentgen ray. If their experiments are confirmed they will have a very direct bearing on the explanation of the delayed rise in systolic blood pressure and its relation to the testing of the heart's functional capacity. They showed that during moderately heavy work the heart increases slightly in size and a few seconds after work suddenly becomes smaller than normal. The increase during work they attribute to the greater quantity of blood pumped into the heart by the muscular and respiratory activity incident to work. They also offered proof that the heart completely empties itself at each systole of this much increased content, whereas the heart of a resting person expels only about one-half of its contents at each systole. The increase in size during work is not to be regarded as a sign of insufficiency because the heart expels its entire content at each systole. Only if a greater quantity of blood than normal remains in the heart after systole does an insufficiency exist. The rapid diminution in size of the heart immediately after work is attributed to the sudden decrease in the quantity of blood pumped into the heart resulting from the stopping of muscular activity.

<sup>2</sup> Cannon. *Am Jour Physiol*, 1914, xxviii, 356. Von Anrep. *Eng Jour Physiol*, 1913, xlv, 318. Hooker. *Am Jour Physiol*, 1911, xxviii, 235. Schneider and Havens. *Am Jour Physiol*, 1915, xxxvi, 239.

<sup>3</sup> Nicolai and Zuntz. *Berl klin Wchnschr*, May 4, 1914, p. 821.

Our own experiments and the facts of circulatory physiology already adduced together with the observations just quoted, give us some insight as to the cause of the delayed rise in systolic blood pressure following work. It may be stated as follows:

In normal people during heavy work the systolic pressure mounts rapidly and the left ventricle finds it more and more difficult to expel its contents against this increasing resistance. At a certain height of aortic pressure the ventricle probably does not empty itself completely and a steadily increasing volume of blood remains in the heart after each systole. In other words, an insufficiency exists. At this moment the Roentgen ray would possibly show a heart decidedly increased in size instead of slightly increased, as found by Nicolai and Zuntz during moderate work. If the work stops the vessels of the splanchnic area begin to relax and the blood pressure falls. Now the heart works more efficiently against the lowered aortic pressure and expels a larger quantity of the increased residual blood at each stroke, until finally it empties itself completely with each systole. The increased quantity of blood which the recovering heart thus throws into the aorta more than compensates for the pressure-lowering effect of the dilating splanchnic vessels and the pressure rises briefly, thereby producing the delayed rise in blood pressure.

The different course of the curve of the blood pressure *during* the work period in patients with cardiac insufficiency implies a difference in circulatory mechanics in these patients as compared with normal persons. This curve showed a slight rise and often a fall with increasing work. The curve *after* work was the same as in normal individuals, except that much smaller amounts of work produced the delayed rise.

The splanchnic vessels in these persons presumably contract during work in the same way as in a normal person. The failure of the blood pressure to rise decidedly during work shows that the heart must propel, if anything, less blood per minute into the aorta than when at rest, even though the rate is much increased, otherwise with a narrowed stream-bed and the same volume discharged per minute the pressure would rise.

Nicolai and Zuntz claim that during work much greater quantities of blood flow into the heart and are ejected at each systole. In our experiments the heart could not have expelled these increased quantities of blood or, as we have already said, the pressure would have risen. Therefore, the blood must have accumulated in the heart and produced a dilatation or insufficiency. The narrowing of the stream-bed caused by the splanchnic constriction incident to work must also play a part in producing this insufficiency.

When the work stops, the stream-bed resumes its normal proportion, possibly more slowly than in a healthy person, the heart acts more efficiently, and expels the increased residual blood, which is sufficient to produce a rise in blood pressure. If the heart is much dilated it probably requires a short time to reach its maximum efficiency and expel its increased content and we have a slowly mounting blood pressure. In other words, our "delayed rise in systolic pressure"

Therefore, if we accept this tentative explanation of the circulatory physiology of exercise, a delayed rise in systolic pressure after work in a normal person or in one with cardiac insufficiency would mean that the preceding work had either made the heart temporarily insufficient or had increased an already existing insufficiency.

Our *clinical experiments* demonstrate conclusively, we believe, that in the pulse rate and blood pressure reactions to graduated work we possess a valid test of the heart's functional capacity. If the systolic blood pressure reaches its greatest height not immediately after work but from 30 to 120 seconds later, or if the pressure immediately after work is lower than the original level, that work, whatever its amount, has overtaxed the heart's functional capacity, and may be taken as an accurate measure of the heart's efficiency.<sup>4</sup>

Graupner<sup>5</sup> in 1906 carried out a large number of experiments on normal people and persons suffering from cardiac insufficiency, using a Zuntz ergometer and employing the method of frequent blood pressure readings before, during and after work. He reached the following conclusions:

"1 Moderate work in powerful persons causes no change in the systolic blood pressure after work.

"2 An increase in work causes a rise in the systolic blood pressure immediately after work and this returns quickly to normal. Repetition of the work causes the blood pressure to rise less high and to return more quickly to normal.

"3 If the work is still more increased we find directly after work a *sinking* of the blood pressure. Yet the blood pressure then rises quickly above normal and then falls back to normal. This primary fall of the blood pressure and secondary rise above normal is characteristic of 'functional insufficiency' of the heart.

"4 If the blood pressure after work is lower than normal and then slowly returns to normal, but does not rise *above normal*, a primary

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4 The determination of delayed rises in patients suffering from auricular fibrillation is difficult and inexact. We have taken the first well-marked beat heard at each reading as a guide. Here the increase in heart-rate is an important aid in deciding if the preceding work has overtaxed the heart.

5 Ztschr f exper Path u Therap, 1906, III, 113, Deutsch med Wchnschr, 1906, No 26.



myocardial weakness exists. This reaction is characteristic of pathological insufficiency."

By the term "normal pressure" Graupner presumably meant the pressure when it had reached a constant level just previous to the work. Apparently he did not take the pressure before each experiment. The amounts of work performed in his experiments were about the same as in ours. His blood pressure readings were all made by palpation and he generally made three or four in the course of thirty or forty seconds without letting the air out of the cuff.

We were able to corroborate his first conclusion and the first half of his second conclusion. His fourth conclusion we found true in a very small number of patients with cardiac insufficiency. His remaining conclusions, which constitute the essential features of his test, we were unable to confirm.

Graupner's failure to measure the pressure before each experiment explains to a certain extent the divergence of our results, for the pressure may be as much as 20 mm. of mercury lower before the last experiment than before the first. Also the error inherent in the palpatory method of taking blood pressure especially if the arm be compressed for 30 seconds is considerable and may explain some of our differences.

#### METHOD OF PERFORMING OUR TEST OF THE HEART'S FUNCTIONAL CAPACITY

The apparatus used consists of pairs of 5, 10, 15 and 20 pound dumb-bells, and a steel bar about 40 inches long weighing 25 pounds. Two types of movements are done with the bells.<sup>6</sup> In the first a pair of dumb-bells is held at the shoulders, one in each hand, and then pushed alternately above the head and toward the median line until the arms are fully extended. As one bell moves up fairly rapidly the other bell returns to the shoulder, the two moving in a sort of see-saw rhythm. In the other movement a bell is held in each hand, the arms hanging by the side of and close to the body, and then each forearm is alternately flexed, raising the bell to the shoulder. The patient stands or sits according to his condition. But one movement is performed with the steel bar. It is picked up from the floor with both hands, raised first to a level with the shoulders, then pushed above the head until the arms are fully extended and then quickly lowered to the floor again with a single rapid motion.

It is possible to calculate approximately the number of foot-pounds of work performed in each of these movements. There is a certain amount of work, however, which we cannot estimate in foot-pounds.

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<sup>6</sup> These movements were first described by Dr. Jacob Teschner of New York.

When a patient stands with a pair of dumb-bells at his shoulders without moving them, work is done as shown by his circulatory reactions, but we cannot estimate it in foot-pounds. This unknown factor can be ignored, however, for our purpose.

More adults average 2 feet as the distance through which a bell is pushed from the shoulder to full extension of the arm. In the flexion movement, the distance through which the bell is carried from the side of the body to the shoulder averages from 2 feet to 2 feet 6 inches. Now if a 5-pound bell is pushed through 2 feet, 10 foot-pounds of work are done. If the total number of pushes are twenty, 200 foot-pounds are done. For the sake of comparison, the time it takes a patient to do any quantity of work should be noted.

If the patient whose heart is to be tested has but recently recovered from an attack of cardiac insufficiency, it is well to start with a pair of 5-pound bells, the patient sitting on a stool. Two hundred foot-pounds of work are then given either by flexing or extending the bells. The pulse rate and blood pressure are taken every thirty seconds according to the examples given on a preceding page. After the pressure and pulse have returned to the original, 300 or 400 foot-pounds are done in the same way. The work is increased with each experiment until we reach a delayed rise in blood pressure. *The experiment which has caused a delayed rise should always be repeated after a few minutes' rest, with a slightly increased amount of work, for the purpose of confirmation.* When once the amount of work which will produce a distinct delayed rise in blood pressure is ascertained, it is quite remarkable how little the results vary on a repetition of the experiment with the same or increased work. Yet if our test is valid this should be so.

The following examples illustrate this point.

This patient was 64 years old and suffered from aortic regurgitation and cardiac insufficiency.

Time	Pulse Rate	Systolic Blood Pressure
3 45	80	132
160 foot-pounds (10 lb bell extended 8 times)		
3 46	88	138
46½	80	134
47	80	134
47½	80	132
48	80	134
49	80	134
3 55	80	130
200 foot-pounds (10 lb bell extended 10 times)		
3 56	88	142
56½	84	146
57	80	142
57½	76	122
58	76	136
59	80	132
4 03	80	130

Delayed rise {

240 foot-pounds (10 lb bell extended 12 times)			
4 04	88	Delayed rise	136
04½	84		142
05	84		138
05½	80		144
06	80		144
06½	76		138
07	80		144
08	76		134
09	76		128
4 13	76		130

As a general rule a patient's cardiac capacity will vary but slightly from day to day. If he improves in general condition his cardiac capacity increases, and if he retrogrades it decreases. Lack of sleep or transient infections have very prompt and decided effects on the cardiac capacity, particularly in persons who already have damaged hearts.

The following examples illustrate this point.

July 7 a patient with a mitral lesion and cardiac insufficiency showed the following reaction (he had been able to do between 600 and 900 foot-pounds each day but not more, during the three weeks previous to this date)

Time	Pulse Rate	Systolic Blood Pressure
11 15	92	120
750 foot-pounds in 40 seconds (15 lb bell, extended 25 times)		
11 16	116	128
17	104	130
18	96	128
19	96	124
20	96	124
22	100	124
23	92	120
900 foot-pounds in 40 seconds (15 lb bell flexed 25 times)		
11 26	116	138
27	108	130
28	96	126
29	96	116
30	96	122

On the afternoon of July 7 the patient became very angry, so much so that he "trembled for three hours afterward." That night he slept but a few hours. On July 8 he showed these reactions:

Time	Pulse Rate	Systolic Blood Pressure
11 37	92	124
375 foot-pounds in 20 seconds (15 lb bell flexed 10 times)		
11 38	104	136
39	96	136
40	92	132
41	90	126
42	98	130
43	96	128
44	92	126
45	92	122
46	96	120

560 foot-pounds in 25 seconds (15 lb bell flexed 15 times)			
11 47	108	Delayed rise	120
48	104		134
49	104		134
50	104		134
51	100		130
52	96		124
12 01	96		120
725 foot-pounds in 30 seconds (15 lb bell flexed 20 times)			
12 03	108	Delayed rise	126
04	104		130
05	96		130
06	100		132
07	104		130
08	96		128
09	92		124
10	96		120

July 9 he was again able to do 750 foot-pounds and July 30 he did 1,400 foot-pounds in sixty seconds

Another patient suffering from renal tuberculosis and a stricture, but with a normal heart, had lost much weight and sleep, being obliged to pass urine every hour

May 11, 600 foot-pounds of work caused a delayed rise in blood pressure. His stricture was then relieved, he began to sleep normally, his appetite returned and he was able to take daily walks. May 21, 1,500 foot-pounds of work were performed before a delayed reaction ensued

Rarely we find that our results are not unvarying. We have records of one man with a presumably normal heart who showed a very distinct delayed rise with 640 foot-pounds of work performed in twenty-two seconds, and thirty minutes later did not show a delayed rise until about 1,300 foot-pounds of work in twenty-five seconds had been done

*The Testing of Patients Whose Cardiac Capacity Exceeds an Ability to Perform 1,000 Foot-Pounds of Work in 60-90 Seconds—* People with normal hearts, or patients with well compensated heart lesions, afford a more difficult problem in mechanics when their hearts are functionally tested. These people are able to flex or extend heavy dumb-bells until their arm muscles are exhausted and yet the heart muscle will show no exhaustion. That is, no delayed rise in the systolic blood pressure is obtained. Here it is necessary to use more powerful muscles, capable of doing much greater amounts of work, in order to tire the heart. We use in these people the 25-pound steel bar which is lifted from the floor to the shoulder and above the head until the arms are fully extended. Then it is lowered quickly to the floor and raised again above the head. An adult will raise the bar between 6 and 7 feet, performing thus between 150 and 175 foot-pounds with each raising. In addition to the work arising from the bar movement, the raising of the trunk of the body each time from a

stooping to an erect position is equivalent to a certain number of foot pounds. The exact number is very difficult to estimate, but from some comparative experiments we are now carrying out it apparently lies between 40 and 50 per cent of the body weight. That is, a man who weighs 150 pounds does between 60 and 75 foot-pounds of work each time that he raises his body from a stooping to an erect position.

The testing of these hearts is necessarily at the present time a comparative matter, and we are unable to obtain absolute values, unless we have a bicycle ergometer at our disposal.

One example of these normal cases will be given.

Male, adult, aged 41, weighing 160 pounds, with a normal heart

Time	Pulse Rate	Systolic Blood Pressure
8 36	68	112
800 foot-pounds (20 lb bell pushed 20 times)		
8 35½	84	120
36	72	122
37	66	120
38	66	116
39	66	118
43	66	110
1,000 foot-pounds (20 lb bell pushed 25 times)		
8 45	84	124
45½	72	120
46	72	112
47	72	110
55	66	112
2 400 foot-pounds (approximate) (25 lb bar lifted 7 feet 10 times)		
8 56½	108	{ 134
57	84	{ 136
57½	66	116
58	66	114
59	66	112
3,360 foot-pounds (approximate) (25 lb bar lifted 14 times)		
9 01	114	{ 136
01½	84	{ 138
02	72	130
03	76	126
04	66	114
4,800 foot-pounds (approximate) (25 lb bar lifted 20 times)		
9 08	120	{ 136
08½	90	{ 146
09	78	136
10	72	130

#### SUMMARY

A large number of experiments have been carried out on normal persons and those suffering from cardiac insufficiency to determine the effect of graduated work on the pulse rate and systolic blood pressure. The work was performed by means of a Krogh bicycle ergometer in a few persons and by dumb-bell exercises in the majority of subjects.

It has been demonstrated that a certain form of the curve of systolic blood pressure determined *after* the completion of work is characteristic of an overtaxing of the heart's functional capacity

A tentative explanation has been given of the circulatory physiology of exercise (work)

A practical test for estimating the heart's functional capacity has been described

It is a pleasant duty to express our thanks to Dr Horatio B Williams of the Department of Physiology of Columbia University for his assistance in supervising the experiments conducted with the bicycle ergometer, and for many valuable suggestions made during the course of the work outlined above. Also we are indebted to Mr R McIntosh for much help in the experiments with the ergometer

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# SOME ATTEMPTS TO PRODUCE EXOPHTHALMOS EXPERIMENTALLY<sup>1</sup>

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In a paper<sup>1</sup> published in 1914 I endeavored, on the basis of a number of clinical and experimental observations, to make a contribution to our knowledge of the pathogenesis of the eye symptoms in exophthalmic goiter. I dwelt in that connection particularly on Landstrom's explanation of their origin, and, making reference to our present anatomic and clinical information, expressed my doubts as to the possibility of maintaining Landstrom's theory. The chief points on which I based my remarks were the following:

1 The "Landstrom muscle," or rather the *musculus capsulopalpebralis* (Hesser<sup>2</sup>), is so weak and so asymmetrically placed as to be hardly capable of producing alone the pronounced eye symptoms which are not infrequently observed in exophthalmic goiter. Above all, it is difficult to understand how a contraction of that muscle should produce a pronounced shifting forward of its posterior origin (of the region about the equator of the eyeball), and thus of the entire eyeball, and not a shifting back of its anterior origin (*septum orbitale* in the eyelid), since the former is a point considerably more fixed than the latter. Sattler<sup>3</sup> and Hesser have given grounds in their anatomic investigations for these views and have emphasized their importance.

2 Even when we assume that the smooth muscle in the orbit can shift the bulb in a forward direction, we encounter great difficulties in trying thus to interpret the genesis of the eye symptoms in exophthalmic goiter. For, assuming that the contracted condition of the muscle that would produce them is directly the result of a stimulation of the supplying nerve—the sympathetic—we must not overlook among other things two of the peculiarities of the exophthalmic goiter syndrome. In the first place, the eye symptoms, as I have found, in 10 per cent of the cases, are rather frequently on one side only, in the second place, the pupillary signs are not a part of the regular exophthalmic goiter symptoms and may, even in extreme exophthalmos of that disease, not be observed at all. The one-sided nature of the eye symptoms is extremely hard to understand, if we accept Moebius' theory that the nature of exophthalmic goiter is chiefly that of an intoxication of the sympathetic nervous system, by poisonous decomposition products disseminated by the general circulation from the thyroid gland. And the absence of pupillary symptoms is in equally great measure incomprehensible if we accept the opposite view of the origin of the sympathetic stimulation, that it is a more direct, mechanical effect of a thyroid enlarged on one or both sides of the nerve. For we must then inquire why

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1 Troell, Abraham. *Mitt a d Grenzgeb d Med u Chir*, 1914, xxvii, 418

2 Hesser. *Anatomische Hefte*, 1913

3 Sattler, in Graefe-Saemisch. *Handbuch der gesamten Augenheilkunde* 1911, Ber u d 37. *Versamml d Ophth Gesellsch*, Heidelberg, 1911, Wiesbaden, 1912, p 181

an effect of such limited compass should exercise no stimulation on those fibers in the cervical sympathetic that run to the smooth muscle of the eyeball (*musculus dilatator pupillae*), but should affect only those that go to the smooth muscle of the orbit (*musculus capsulopalpebralis*), since it is well known that an electric stimulation of the cervical sympathetic always produces in man, as well as in related animals, chiefly a dilatation of the pupil, with a widening of the lid-cleft and possibly a bulging out of the eyeball, while conversely, the cutting of the sympathetic cord will produce corresponding paralytic symptoms in both these muscular tracts (contraction of the pupil, narrowing of the lid-cleft, etc.)

Logical as the foregoing reasoning may be, it suffers from the imperfections of our present anatomic and clinical knowledge. Perhaps the future may disclose data that will show this chain of evidence to be not equivalent to a full proof. Possibly the eye symptoms in exophthalmic goiter are produced by toxic influences similar to those we have reason to believe are present in the "system diseases" of the central nervous system, or to those which enable a poison, like amyl nitrite, on being inhaled to affect the vagus fibers that proceed to the heart, but not those that proceed to the digestive tract. Hesser,<sup>4</sup> in a recapitulatory article of recent date, has emphasized the conditions produced by amyl nitrite. He suggests the possibility that the exophthalmic goiter toxin may produce exophthalmos in man by influencing certain nerve elements running to the orbit, in a manner resembling that of amyl nitrite which preferably affects the cardiac vagus fibers.<sup>5</sup> But we must point out that neither this analogy nor the analogy with the behavior in nervous "system diseases" for the present is of great value in determining to what extent the absence of pupillary symptoms in exophthalmic goiter militates against Landstrom's theory of eye symptoms. For, applied to the phenomena in exophthalmic goiter, such an analogy would imply the possibility that the toxins of the thyroid gland, disseminated by the circulation, should be able for a protracted period, to influence *only* on *one* side, *some* of the sympathetic fibers, or of the sympathetic ganglion cells (those belonging to one *musculus capsulopalpebralis*). Such a hypothesis, in view of our present state of medical knowledge, constitutes a quite peculiar and unsatisfactory complication of the problem.

If one accepts my reasoning as to the significance of the regular occurrence of pupillary symptoms on electric stimulation of the sympathetic, but their absence in typical exophthalmic goiter, one is confronted with a new question. May not valuable data on the genesis of exophthalmos be obtained *from attempts to produce exophthalmos experimentally, without the mediation of the cervical sympathetic?*

It would seem possible to make an attempt to produce exophthalmos by the use of toxic materials, in some cases without any preparatory measures, in others, after having removed the superior cervical sympathetic ganglion *on one side*. If in the latter case, it should be found that exophthalmos failed to appear on the side on which the interruption had been made in the sympathetic, this would be proof

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4 Hesser Hygiea, 1914, lxxvi, 561

5 Unfortunately he gives no citation of authorities, a circumstance all the more to be deplored since it is characteristic of his entire paper, which otherwise is illuminating. I have, therefore, not been able to determine whether in the investigations under consideration any reliable observation of the fact could be made, that the vagus fibers of the digestive tract remained unaffected.



that the cooperation of the sympathetic is necessary for the production of such exophthalmos, such an outcome of the experiment would thus lend a certain support to Landstrom's theory. But the opposite would be the case if it should be as easy to produce exophthalmos in an individual whose sympathetic ganglion had been removed so long ago that the nerve fibers situated distally to it—the postganglionic fibers—should have degenerated.

The chief difficulty about the procedure mentioned above is the well-known great difficulty in producing exophthalmic goiter and exophthalmic goiter exophthalmos experimentally. Souppalt probably was the first (1897) to undertake experiments in this direction. He has had many successors, but a study of the literature on the subject gives one the decided impression that the experiments thus far made on animals have only in exceptional cases given rise to an unmistakable protrusio bulbi, no matter what procedure has been followed. The results have been very uncertain, both in cases in which injection of thyroid juice has been resorted to, and in cases of transfer of normal thyroids, goiters, exophthalmic goiters, thymus, etc.<sup>6</sup>

I have, therefore, believed that I should be more likely to obtain results if I should try first and foremost other toxins than those of the thyroid gland and the like in producing exophthalmos. One such, beta-tetrahydronaphthylamin, first used by Stern,<sup>7</sup> has long been known as having a direct affinity with the sympathetic nervous system, and as giving, on subcutaneous injection into animals, symptoms of stimulation from the muscles innervated by the sympathetic nervous system. In cats it produces, among other things, dilatation of the pupil and protrusion of the bulb (Elliot<sup>8</sup>). It would, therefore, be particularly applicable in the investigations I have in mind. But the drug has the disadvantage of being very difficult to obtain commercially at this time. This is not true to so high a degree of another chemical substance, paraphenylenediamin (which Hesser mentions casually in his latest paper). Just how we are to regard the effect of paraphenylenediamin is not known. Probably it does not work directly through the nervous system. Other drugs having a sympathicotonic effect are known, as epinephrin and cocain. Yet their availability for

6 An historical résumé of these experimental investigations is found in Klose (*Ergebn d inn Med u Kinderheilk v Kraus u a*, 1913, x, 167). Of later investigators who claim to have succeeded in producing exophthalmos in animals, there may be mentioned Baruch (*Centralbl f Chir*, 1911, xxxviii, 1185, *ibid*, 1912, xxxix, 316) and Bircher (*Centralbl f Chir*, 1912, xxxix, 138). See also Biedl (*Innere Sekretion*, 1913, i, 212) and Kempner (*Centralbl f d Grenzgeb d Med u Chir*, 1914, xviii, 347).

7 Stern *Virchows Arch f Path Anat*, 1889, cxv, 14.

8 Elliot *Jour Physiol*, 1912, xlv, 374.

our present purpose may be considered negligible. It is, in fact, interesting to note that the subconjunctival injection of two such extremely sympathicotonic substances, in spite of the situation near the surface of the capsulopalpebralis muscle, does not produce a bulging of the eyeball of even 1 millimeter, but may, on the other hand, bring about a striking widening both in the pupil and in the lid-cleft. This tells, in its way, against the probability that exophthalmic goiter exophthalmos may be the effect of a stimulation of the sympathetic (Sattler<sup>9</sup>).

Paraphenylenediamin on subcutaneous injection into the sacral region of dogs and monkeys, by Grunert,<sup>10</sup> Birch-Hirschfeld<sup>11</sup> and others, has been found to produce a symptom group including among other things increased epiphora and mucous secretion, chemosis, injection of conjunctiva, increase in intra-ocular pressure, and exophthalmos, the anatomic cause of the latter is a drenching of the orbital tissue with serous fluid.

I repeated these experiments with paraphenylenediamin hydrochlorid Merck (paradiaminobenzene hydrochlorid) on various kinds of animals, sometimes under entirely normal conditions, sometimes after removing the upper sympathetic neck ganglion. An account of these experiments is given in the accompanying table and additions.

For considerations of space, I have limited myself, with regard to my experiments on dogs, to a short tabular synopsis, as, moreover, the symptoms observed by me after paraphenylenediamin injection coincide in the main with those obtained previously by other investigators.

In addition to the upper sympathetic cervical ganglion, in each case in which that operation was performed, from 2 to 3 cm. of cord under it was also removed.

The operative procedure for removing the ganglion is preferably the following. An oblique transverse incision is made corresponding to the base of the skull, beginning right under the easily felt bulla ossea ossis temporalis, in front of the atlas and the muscles originating from that point. The incision is continued downward toward the median line. Laterally behind the large vessels of the neck, the vagus is easily found. In the dog, the sympathetic fibers run along the neck like a fine nerve laterally behind the vagus and in intimate contact with it, the two nerves being enclosed in one common sheath of connective tissue, in the cat, the sympathetic is easily distinguished from the vagus with naked eye, in the rabbit the fibers often run in two separate bundles on either side of the neck. The ganglion cervicalis superior is in dogs very difficult of access for operative purposes. It lies far up toward the base of the skull, on the musculus longus capitis, medially behind the plexus nodosus nervi vagi. Its size is not inconsiderable, usually at least 3 or 4 millimeters in length. Its color is more decidedly bluish-gray than that of the vagus. It is connected

9 Sattler. *Munchen med. Wchnschr.*, 1911, LVIII, 2307, Deutsch. *med. Wchnschr.*, 1912, p. 93.

10 Grunert. *Ber. u. d. 31. Versamml. d. Ophth. Gesellsch.*, Heidelberg, 1903, p. 208.

11 Birch-Hirschfeld, in Graefe-Saemisch. *Handbuch der gesamten Augenheilkunde*, IX, Chapter XIII, 100.

# PARAPHENYLENEDIAMINE EXPERIMENTS ON DOGS \*

Number	Dog's Weight, Kg	P D Dose per Kg Body Weight, Gm	Eye Symptoms										Other Local Symptoms	Changes in the General Condition					Postmortem Findings			
			Lipphora	Edema in Nictitating Membrane	Edema in Conjunctiva Palpebrarum	Edema in Conj Oculi	Hyperemia in Conjunctiva	Pur Conjunctivitis	Increased Depth of the Anterior Chamber	Increased Intra Ocular Pressure	Protrusio Bulbi	Increased Salivary Secretion		Swelling in the Submaxillary Region	Unrest	Sluggishness	General Appearance of Being Very Sick	Vomiting		Diarrhea	Convulsions (spasms)	Death
1	4.2	0.075	+		+	+					+	+	+	+	+	+	+	+	+		Brown pigmentation of lacrimal and submax glands. Edema in these glands and in the neck lymph glands. Dog died following day during sympathetic operation	
2	5.0	0.075+ 0.075		+	+									+	+	+	+			+	+	Lacrimal glands much brown pigmented
3	8.185	0.075	+	+	+	+	+	+						±	+	+		+	+	+	+	Hardly any edema visible in the conjunctivae
4	5.1	0.1 0.1		+	+		±	+		+	+				+	+	+	+	+		+	
5	3.975	0.1		+	+						±							+	+	+		(Decalcifying of the orbits, microscope examination of orbits and orbit contents)
6	13.15	0.08		+			+				+				+	+	+					
7	2.95	0.08		+	+						+					+	+			+	+	
8	6	0.09	+	+	+			+		+	+				+		+			+		Eye symptoms still visible, but less evident (Microscopic examination of the orbits with contents after decalcifying)
9	6	0.06	+	+	+					+	+			+		+				+		Also the submaxillary region was swollen and edematous (Orbits decalcified and microscopically examined)
10	6.56	0.04 0.04		+	+	±	+				±						+			+	+	
11	15.98	0.05			+	+			+		±						+			+		No pigmentation of the submaxillary glands
12	8.84	0.05										+			+	+				+		(Orbits, with contents, decalcified, and examined microscopically)

\* The sign ± indicates that the symptom in question was only slightly present.

REMARKS

Two hours previous to this injection, the same dose P D had been injected in 2 per cent boric acid solution. As this did not produce any effect, the injection was repeated, 25 per cent water solution being used and sterilizing being performed by boiling (for all the following cases, P D was used in this manner). The eye symptoms appeared three-fourths hour after injection, and were evidently increasing during the five hours following. Yet protrusio bulbi was not marked until the day after, the conjunctival edema then having disappeared. The latter day, ganglia cerv sup were removed.

Two hours previous to the first injection, right sup cerv symp ganglion had been removed. The first injection of 0.42 gm P D only produced some conjunctival edema, particularly in the right eye. Therefore the same dose P D was injected once more, 3½ hours later. The edema now following was, after 2½ hours, more pronounced on the right side than on the left, dog died shortly afterward.

The day following the injection, the dog was somewhat more lively. Then the left cerv sup symp ganglion was removed. Dog died shortly after.

One week after the injection, every general and local symptom had disappeared, except some corneal opalescence which had been visible for about four days. Left sup symp cerv ganglion was removed. On the third day after that (when no symptom from the first injection was to be seen any longer), the same dose P D (0.56 gm) was injected. At this time the dog did not develop any eye changes but only general symptoms, death followed soon.

Three and one half hours after the injection the dog was etherized. Cannulas were inserted into the right femoral artery and vein, and the dog was bled to death. The whole vascular system was carefully washed out with 0.1 per cent salt solution. A cannula was inserted into the thoracic aorta, and 5 per cent liquor formaldehydi was injected in direction toward the head, thus establishing a good hardening in situ of the orbit contents.

Four days later when all eye symptoms had disappeared and the dog seemed quite well, the left sup cerv symp ganglion was removed. The dog died during the operation (from much pulling on and hurting the vagus—respiration paralysis).

One hour after the injection there was a pronounced bulging of the bulbs which with its staring look and almost complete fixity of the bulbs was very much like exophthalmos in exophthalmic goiter. Only a careful examination revealed the edema of the nictit and conjunctival membranes. This edema increased very much during the two hours preceding death.

Two days previous to the injection, the left sup symp cerv ganglion had been removed. This caused lessening of left pupil and lid cleft, and enophthalmos sin. Two hours after the injection the eye symptoms (edema of the nictit and conjunctival membranes) were more pronounced on the left than on the right eye. Five hours after the injection the eye symptoms were equally present in both eyes, now there was also to be seen a bulging of the bulbs, as well as much fixity of them, the pupils were of medium and equal size.

Two days previous to the injection, the left sup symp cerv ganglion had been removed (which had produced the same paralyzing symptoms as in Case 8). The eye symptoms following the injection developed their maximum 3½ hours after the injection, having been increasing a little slower on the right side than on the left. Left pupil was very narrow all the time, right pupil very wide.

Four days previous to the injection, the same ganglion operation was done as in Cases 8 and 9, and with the same effect. During the first hours following injection, the eye symptoms were more pronounced on the left side. Later on, there was no evident difference between these changes on either side. Yet the symptoms remained longer on the left side than on the right, still a week later there was some conjunctivitis on the left eye. Seventy-one days after the ganglion extirpation, left pupil still was small (and elliptical in vertical direction), slowly reacting, left lid cleft was just a little narrower than right, enophthalmos sin was not unquestionable. Another P D injection was done. Eye symptoms developed, but more pronounced on the left side than on the right, though not even on the former very strong. Death followed soon.

Ganglion cerv symp sup sin was removed sixty-four days previous to the injection. Paralyzing effect as in earlier cases (and also purulent conjunctivitis sin). Two days later the epinephrin test of Loew was negative on both eyes. Three weeks later the symp paralyt symptoms were, on one day, less pronounced than before that time, once the pupil was found elliptical in a vertical direction. Two months later the paral symptoms (even the enophthalmos) were very evident. The inj symptoms reached their maximum 6 hours after the injection, equally pronounced on both eyes, death occurred some hours later.

One hundred and eleven days previous to the operation, the left phrenic nerve had been cut (as far down in the neck as possible), whereupon its proximal end had been turned upward and sewed to the distal end of the sympathetic (which also had been cut, close below the superior ganglion). At the necropsy the nerve suture was nicely healed and not to be detected. The dog had all the time showed paralyzing symptoms on the left eye (small pupil, small lid cleft, pulling forward of the nictit membrane and enophthalmos, yet the latter had by and by become less pronounced).

below by a number of its branches with the vagus, from which it is difficult to separate them. When the sympathetic cord has entered the thoracic cavity, it forms the ganglion cervicalis inferior and separates from the vagus.

In addition to these experiments on dogs, I have also made injections of paraphenylenediamin on a cat, a rabbit and a guinea-pig. The results obtained were not, as the report below will show, entirely similar to those obtained from dogs.

CAT 13—Weight 3,390 gm. Nov. 16, 1914, received subcutaneous injection in lumbar region of 0.25 gm. of paraphenylenediamin (0.075 gm. per kilogram body weight). Immediately after this the pupils were small and reacted to light, cat was sluggish and discontented. Two hours after injection, pronounced swelling beneath the lower jaw, considerable conjunctival edema, so that the eyelids could not close, no noticeable exophthalmos, pupils of medium size, considerable general depression. The cat died shortly after. Postmortem examination showed much edema in the lower jaw region, as well as subconjunctivally, but nowhere any brown pigmentation. The orbits with their contents were examined microscopically. (In this case as well as with the other animals on which such examination was made—the rabbit, the guinea-pig, and three dogs—the animal's head was first hardened in liquor formaldehydi, whereupon each orbit was sawn out of its place and decalcified in 5 per cent solution of nitric acid, celloidin sections of horizontal and sagittal—and in one dog, oblique—meridians were made of the decalcified specimens.)

RABBIT 14—Weight 590 gm. Nov. 14, 1914, the pupils were wide, equally large and reacting to light, 0.013 gm. of paraphenylenediamin were injected subcutaneously (0.075 gm. per kilogram body weight). No effect whatever was observed within one hour, therefore the same dose was again injected. November 16, no perceptible effect, pupils as before, injection made of 0.135 gm. of paraphenylenediamin. Without having previously shown any noteworthy symptom, the animal one and three-fourths hours after last injection was suddenly attacked by clonic general convulsions, which resulted in death in a few minutes. The necropsy revealed nothing of interest.

GUINEA-PIG 13—Weight 600 gm. Nov. 16, 1914, pupils wide, reacting to light, 0.045 gm. paraphenylenediamin injected subcutaneously. November 17, no perceptible effect, another injection, same dose. November 18, no perceptible effect. November 23, animal still well, killed under ether. Necropsy showed nothing of interest.

From the records of the operations, it is evident that the paraphenylenediamin injection, as far as eye symptoms, particularly exophthalmos, are concerned, gave positive results in the case of the dogs, but a negative result with cat, rabbit and guinea-pig.

The time for the appearance of the symptoms varied, both for the local phenomena and for those of general nature. Usually the dog which had received an injection gave evidences of great unrest, apparently because of pain at the place of injection. Thereupon followed a condition of general dulness. The dog would lie on the floor limp and give the impression of being very sick. In five of the cases occasional vomitings occurred in the next few hours, in three cases diarrhea. Clonic convulsions, especially in the lower jaw, back of neck, and in the extremities, were observed in five animals, usually

continuing until death ensued. In Case 2 there was no typical convulsion, but slight twitches in the extremities, giving the gait a somewhat spastic ataxic appearance. A lowering in blood pressure was observed in Dog 10, the only animal in whose case such a record was made<sup>12</sup>

Eye symptoms failed entirely to appear for several hours in one case (Case 12). The injection was made in the afternoon. I had no opportunity to observe the dog for more than three hours after that, and in the following night he died. In all the other cases, paraphenylenediamin injection in dogs was followed by more or less pronounced changes in the region of the eyes (and in some cases also around the submaxillary gland). These symptoms appeared within from one-half to two hours after injection, reached a maximum during the following four or five hours, and in case of the animal surviving, had usually disappeared in a week. In one dog (Dog 7) within one hour after injection a bulging of the eyeballs was observed, which, with its characteristic staring expression and the almost immovable fixity of the eyeballs, reminded one of exophthalmic goiter. *exophthalmos*, on closer examination there was found an incipient edema in the nictitating and conjunctival membranes which increased decidedly later, and thus made this case rather like the others. The invariable characteristic in these eye symptoms was an edema which, in almost all cases, was first observed in the *membrana nictitans* and the lower *conjunctiva palpebrarum* and then spread to the conjunctival membrane in its entirety, constantly increasing in quantity. In three cases, the eye syndrome was limited to an edema in the nictitating and conjunctival membranes with no (Case 2) or very slight (Case 10—second injection—and Case 11) *protrusio bulborum*. In the other cases there developed, besides the externally recognizable edematous swelling, sooner or later an unmistakable bulging out of the eyeballs, which in a few exceptional cases persisted even after death. In two cases (Cases 8 and 11) the depth of the anterior chamber was increased, in three (Cases 4, 8 and 9) there was found a noteworthy increase in intra-ocular pressure. Often the edematous swelling at

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12 This experiment was carried out at the second paraphenylenediamin injection as follows. The dog was put under ether. A cannula connected with a mercury manometer and with an ordinary registering kymograph was inserted into one of the carotids, whereupon 0.3 gm paraphenylenediamin was injected subcutaneously. Before injection, the blood pressure was about 100-110. Ten minutes later it stood at 80, twenty-five minutes later, when the dog had been permitted to come out of the narcosis in part and no longer lay limp, the figure rose to 110-120 for a few minutes. He was then put into a deeper sleep. After ten minutes, 70 was registered, after which the figure kept at about 80. An hour after injection, the experiment was stopped because of coagulation of the blood in the cannula and supply tube.

the maximum of the changes was so pronounced that the eyelids could not be closed. It was not possible to determine any other anatomic basis for the symptoms than an edematous accumulation in the tissues, in none of the species could any venous thrombosis be histologically demonstrated.

Size and reaction power of the pupils were recorded, but were often difficult to determine precisely, because of the presence of chemosis. Only in one of the animals did they show a change that could be attributed to the injection. In this case (Case 8) the left pupil was contracted before the injection because of operative paralysis of the sympathetic, but five minutes after injection both were of equal and medium size. The reason for this may, in my opinion, be the alteration in the conditions of the circulation resulting from the injection, as is observed, for instance, in glaucoma, in which condition, together with an increased intra-ocular pressure, there is also a widening of the pupils, no longer reacting to light (and where there is no suggestion of interpreting these symptoms as the result of sympathetic stimulation).

Particular mention must be made of the experiments in which one of the upper sympathetic cervical ganglia had been removed before injection. The effect of this operation *per se*—before any injection was made—was of course a paralysis of the muscles within the orbit supplied by the sympathetic bundles, lid-cleft and pupil became smaller, the nictitating membrane was pulled forward toward the pupil,<sup>13</sup> and the eyeball appeared to recede into its socket. The extent of each of these symptoms varied somewhat. The most constant factors were the decrease in the size of pupil and lid-cleft, they were never lacking for a certain period after operation. Less unquestionable were, sometimes, the forward tendency of the nictitating membrane, and enophthalmos. After a few weeks, or at most months, the decrease in the size of the pupil was, as a rule, the only remaining symptom that was completely evident, an adjustment to the normal appeared to have set in, both with regard to the width of the lid-cleft and, above all, the position of the bulb.

Now, what was the nature of the eye symptoms after paraphenylenediamin injection in those animals in which a paralysis of the sympathetic on one side had been practiced? This was noted in seven of the experiments with the following results

- 1 The eye symptoms were never less pronounced on the side of the paralyzed sympathetic than in the other eye

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<sup>13</sup> This symptom was distinctly observable, but not in a pronounced degree, in Cases 10 and 11, more pronounced in Case 12. In another connection I shall probably dwell more exhaustively on the details of these paralytic symptoms.

2 In two cases (Case 2 and Case 10, second injection) in which the animals lived only a few hours after the injection of paraphenylenediamin, the eye changes were somewhat more pronounced on the side on which operation was performed than on that not operated on. The upper cervical ganglion had been removed two hours and seventy-one days, respectively, before the injection.

3 In three cases (Cases 8, 9 and 10, first injection) the eye symptoms, which included *protrusio bulborum* during the hours immediately following injection, were most pronounced on the side on which operation was performed, but did not present any unquestionable dissimilarity between right and left eye at the time of maximum effect. In these cases the injection had been made from two to four days after removal of the sympathetic ganglion.

4 In two cases (Cases 11 and 12) which received injections sixty-four and 111 days, respectively, after production of the sympathetic paralysis, and which resulted in death within twelve hours after injection, no dissimilarities whatever were observed in the eye symptoms of both sides. Yet the symptoms were in the former case very faint, and in the other not quite beyond doubt.

A summary of these data could yield this result. In the first place, *the eye symptoms produced by paraphenylenediamin, which usually include protrusio bulborum, may be brought about without the intermediation of the cervical sympathetic.* No evidence has been offered for supposing that the cooperation of the sympathetic is necessary for producing the eye symptoms, but it has been shown experimentally that the latter is possible even when the injection is made so long after the removal of the upper sympathetic cervical ganglion that the nerve units situated distally to it may be considered to have already degenerated. In the second place, these paraphenylenediamin experiments show that the final effect of the injection, if it is undertaken after one of the cervical sympathetics has been cut out, will still be produced and will be equally pronounced in both eyes, but it develops more slowly and comes out later in the eye on the side on which operation has been performed. The most plausible explanation of this is probably to be found in the fact that the fibers of the cervical sympathetic that go to the vasoconstrictors predominate over those that supply the vasodilators<sup>14</sup>. The bringing about of a sympathetic paralysis has resulted, therefore, among other things, in a dilatation of the corresponding carotid branches on the operated side, which may have involved the opportunity for a more rapid appearance of

14 See, for example, Frank's "Hamodynamische Operationen" in Tigerstedt's *Handbuch der physiologischen Methodik* 1911, II, Part 4, p. 364. Meltzer, S. J., and Meltzer, C. *Am Jour Physiol*, 1903, IX, 147.



the edema, essentially limited to the contents of the orbit which is the chief anatomic effect of a paraphenylenediamin injection

In connection with the investigations described above, I might refer briefly to other experiments which I made with the purpose of producing exophthalmos. Their results were entirely negative, as far as eye symptoms are concerned, but they may nevertheless be of interest. They were based on the assumption that a chronic stimulation of the cervical sympathetic may produce a bulging of the eyeball. MacCallum and Cornell<sup>15</sup> have proved on dogs that a temporary protrusion may be brought about by the application of an electric current to the cervical sympathetic, they were able to make graphic records of the amount of bulging. I tried without success to repeat the experiments on dogs (three cases), cats (three cases) and rabbits (one case), notwithstanding the use of a very strong interrupted current, I obtained hardly any other striking phenomenon than a maximum dilatation of pupil, no unmistakable exophthalmos was produced, though perhaps there was bulging of 1 or 2 millimeters in the case of one cat. I once had occasion to observe a neck operation on a patient in which the corresponding effect was to be noted, electric sympathetic stimulation brought about dilatation of the pupil, but no visible exophthalmos. And in the paper of MacCallum and Cornell,<sup>15</sup> the same observation is mentioned by them from two patients. Jonnesco<sup>16</sup> is the only one whom I have known to announce a positive result of such experiments, on applying a strong electric current to the sympathetic, he noted the appearance of exophthalmos in man.

In order to bring about a chronic sympathetic stimulation, I have made use of the same principle as that successfully employed by Timme<sup>17</sup> on the vagus (mechanical production of pressure neuritis), and also of the procedure long ago practiced by Langley<sup>18</sup> and recently by Cannon<sup>19</sup> in the neck nerves (phrenicosympathicus anastomosis).

Timme, by placing a ligature very gently around each of the vagus trunks above the diaphragm on cats, succeeded in producing a hyperplasia of the mucous membrane in the stomach (on the other hand no increase, but rather a decrease in the function of the stomach). By cutting the phrenic and sympathetic nerves on one side of the neck of a cat, and sewing together the proximal end of the former with the distal (head) end of the latter, Langley obtained a satisfactory union of these two heterogeneous nerves, but did not, even after

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15 MacCallum and Cornell. *Med News*, Oct 15, 1904

16 Jonnesco. *Tr XIII Cong internat de méd*, Paris, 1900. MacCallum and Cornell (Footnote 15)

17 Timme. *Jour Nerv and Ment Dis*, 1913, xl, 311

18 Langley. *Jour Physiol*, 1898, xxiii, 240

19 Cannon. *Am Jour Physiol*, 1915, xxxvi, 363

197 days, observe any changes in pupil, etc., of the corresponding eye, that might point to a functional disturbance of the muscles supplied by the sympathetic. Cannon, however, claims to have observed this in at least one animal within five months after the nerve operation.

In two dogs I exposed one *cervical sympathetic ganglion*, trans-fixed and *ligated* it, *but not very tightly*. The operation on the first animal was performed Dec 5, 1914. Its general condition was very good until death ensued, December 14, the cause of death was pneumonia. The other dog was operated on Jan 16, 1915 and died, also of pneumonia, March 23. Toward the end the latter animal showed falling out of hair all over the body, emaciation, weakness, and (March 19) a sugar tolerance of less than 5<sup>20</sup>. The pulse rate did not rise (March 19 and 20 it was constant at about 100), and bladder urine was free from albumin and sugar at necropsy. Postmortem the stomach proved to be unusually large, and the thyroid microscopically rather rich in colloid.

In these two dogs I could *not*, notwithstanding almost daily examinations, observe *any* other *eye changes* on the side on which operation was performed than those usually produced by sympathetic paralysis, that is, contraction of the pupil and lid-cleft and, in the first few weeks, enophthalmos. Such an effect was what one would naturally have expected for the period following ligation, it was evidence that the nerve connection in the sympathetic had been broken. But it would seem that symptoms of irritation (pressure neuritis) should have been discernible later. The sixty-four-day period during which the second dog lived after ligation is, however, too short a time to justify any final inferences. Although the entire absence of any visible evidence of sympathetic irritation is striking, a longer period of observation might have led to a different result.

In my last series of experiments, discussed in this paper, I cut both the phrenic and sympathetic nerves on one side of the neck and *sewed together, end to end, the proximal end of the phrenic and the distal end of the sympathetic* (or the upper sympathetic ganglion). The operation was performed on four dogs, two cats and one rabbit. Of these, five died within twenty days after operation (of intoxication from narcosis, infection, postoperative hemorrhage, pneumonia). One dog was killed 111 days,<sup>21</sup> one cat 175 days later. I shall give a more detailed statement of these experiments in another paper. Suffice

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20 That is, saccharose, administered by mouth in doses of 5 gm per kilogram body weight, gave positive Nylander and Benedict tests during the following twenty-four hours. The physiologic tolerance for saccharose in tests on unoperated dogs was found by Goetsch, Cushing and Jacobsen to be on an average 10 gm per kilogram body weight (Bull. Johns Hopkins Hosp., 1911, xxii, 165).

21 Included as No 12 in the table.

it here to say that *in no case* was I able to find *any eye symptoms* that could be attributed to a sympathetic stimulation transferred to the smooth muscles of the orbit or of the eyeball. A contraction of the corresponding pupil and a drawing forward of the nictitating membrane continued throughout the period of observation, indicating that the sympathetic nerve had been interrupted. I had daily occasion to observe that no bulging of the eyeball or widening of lid-cleft, or the like, developed. I did not neglect to make repeated precise observations of the behavior of the pupil in broad daylight as well as in direct light. Never was I able to observe any enlarging of the pupil corresponding to the animal's respiration, which Cannon had found in a cat similarly operated on.

This concludes my report on the attempts to produce exophthalmos experimentally. Considered together, they show that whenever they proceeded from the assumption of cooperation through sympathetic stimulation, they were negative, but that in that group of cases in which paraphenylenediamin injections were made for the purpose, they were positive, even when the cooperation of the sympathetic had been eliminated. Thus far they have proved that an exophthalmos—one not resulting from an intra-orbital tumor, or some such cause—may arise without any intermediation of the cervical sympathetic. But we are by no means justified in transferring these results directly to human beings with exophthalmic goiter. On the contrary, it seems to me that my investigations show, among other things, how necessary it is to refrain from erroneous combinations. The temporary but slight forward shift of the bulb which, at least in certain animals, is likely to be produced by a direct electric stimulation of the cervical sympathetic is one thing, the somewhat more lasting protrusio bulbi in dogs after a subcutaneous paraphenylenediamin injection is quite another matter, and exophthalmos in exophthalmic goiter, sometimes continuing for years and occasionally of extremely pronounced character, has peculiarities that make it also a distinct group.

There is much to be said against the assumption that exophthalmos in exophthalmic goiter may be the result of a sympathetic stimulation. The entire aspect of the eye changes in paraphenylenediamin intoxication as a rule makes the impression of disturbance of the circulation, edema, which is by no means the most striking feature of exophthalmic goiter—although there are some similarities between them that are worthy of note (such as palpebral edema occasionally arising in exophthalmic goiter<sup>22</sup>).

22 See Case 9 in the exophthalmic goiter material, previously presented by me (Mitt a d Grenzgeb d Med u Chir, 1914, xxvii, 42)

On the whole, the question of the genesis of exophthalmos in exophthalmic goiter remains unsolved. Yet it must seem all the more desirable that we should acquire a thorough understanding of it, now that we have arrived at a more complete recognition of the importance of distinguishing clearly, both in diagnosis and prognosis, between the syndrome of clinical and pathologic anatomic phenomena which we roughly speak of as exophthalmic goiter.

# THE CLINICAL STUDY OF EDEMA BY MEANS OF THE ELASTOMETER<sup>†</sup>

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The elastometer, an instrument devised by Schade<sup>1</sup> to measure edema, promises to change the study of edema from a subjective one depending on the amount of pitting obtained on pressure, to an objective one, whereby the degree of edema may be expressed in exact terms. Tactile estimation of edema fails not only to give an accurate idea of fluctuations that occur in an edematous area, but by the tactile sense alone, slight and even moderate degrees of edema may pass unnoticed. Indeed, Widal<sup>2</sup> has shown that in the adult an increase in weight up to 6 kilos may occur before edema will be sufficiently marked to be noted by the palpating finger. This figure varies in different individuals under different conditions. Studies in water retention, which have heretofore been done by noting the changes in the body weight or by determining the fluid intake and output, may now be improved by controlling such studies with estimation of edema obtained by the elastometer, for by means of this instrument, one can detect degrees of edema not appreciable by the palpating finger.

*Principle of the Instrument*—(Figure 1) A disk mounted on a perpendicular tactile rod is placed on the skin surface, with the addition of a superimposed weight, the amount of depression caused by the sinking of the weighted disk into the skin and subcutaneous tissue is graphically transferred by a writing lever to a revolving drum, making a characteristic curve. Surrounding this tactile disk, which measures the elasticity, is a set of three similar tactile disks, which rest on the surrounding skin surface, and indicate by a separate lever on the revolving drum any movement of the central disk other than that caused by the addition or removal of the weight. This line is known as the control line and must be straight in order to have the record of any value. Thus, faulty curves caused by disturbing factors can be eliminated by observing the control line.

*Method of Use*—To use the instrument it is necessary that the patient be absolutely quiet. The location selected for taking the reading may be any part of the body surface overlying a bony area. Thus, the dorsal fold of the wrist, the forehead, or the lower part of the leg above the malleolus, may be used in making these determinations. The dorsal fold of the wrist has been found to give the most satisfactory readings, since this part of the body is more easily put at complete rest than the other areas mentioned. The patient

\* Submitted for publication Oct. 20, 1915.

<sup>†</sup> From the Otho S. A. Sprague Memorial Institute Laboratory of The Children's Memorial Hospital.

1 Schade, H. *Ztschr. f. Exper. Path. u. Therap.*, 1912, xi, 369.

2 Widal, F., and Lemierre, A. *Ergebn. der inn. Med. u. Kinderh.*, 1909, iv, 523.

may be either in the recumbent or sitting posture. The hand and forearm are surrounded by sand bags in such a manner as to give complete relaxation, yet be well immobilized and not interfere with the circulation. The patient must relax as completely as possible. It is almost impossible to obtain readings on patients who will not cooperate. The patient relaxed, the instrument is placed on the table close to the bedside, if the patient is recumbent, or placed on the same table as the extremity tested if the patient is in a sitting position.

The tactile disks are lowered until they come in contact with the skin surface, the disks being so arranged that the control disks surround the weight-bearing disk. This arrangement occasionally offers some difficulty, in that the writing points controlled by these two sets of tactile disks may come in close approximation on the drum surface, thereby hindering their independent

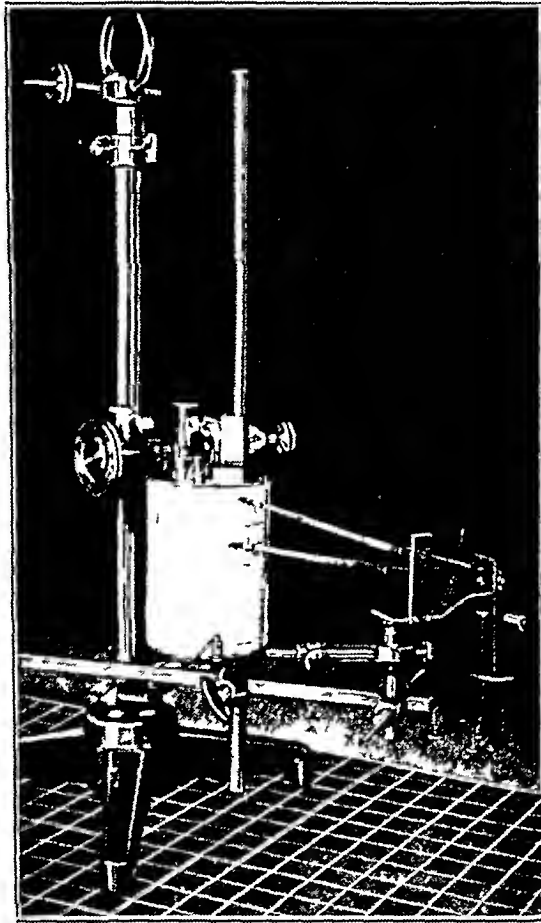


Fig 1—The elastometer

working. Manipulation of the tactile disks is then necessary until the two writing points are separated and the movement of the one does not affect that of the other. The drum is then allowed to revolve. As soon as the lines drawn on the revolving drum are parallel and fairly horizontal, the weight is placed on the weight holder, which is a circular shelf attached to the central rod. These weights are of three sizes, 50, 75 and 100 gm, respectively. In our work, the 50 gm weight has been used almost exclusively, because we found it gave the most satisfactory curves in the majority of cases. The 75 and 100 gm weights are heavier than necessary to obtain successful readings in working with children.

Various degrees of elasticity give characteristic curves. Figure 2 represents diagrammatically extremes of variation in the curves that may be theoretically obtained. Curve 1 represents perfect elasticity. *a* is the base line. At the

point  $x$  the weight is added, whereupon the lever makes its ascent on the line  $b_1$  which reaches its height rather quickly and continues along the line  $b_2$ . At the point  $y$ , the weight is removed and the lever falls rapidly and perpendicularly making the line  $c_1$  and reaches its base line at  $c_2$ , which is on a level with the original base line  $a$ . Curve 2 represents a condition present in a severe edema. At the point  $x$ , the weight is added, whereupon the lever rises rapidly along the line  $b_1$  but soon changes to a slow sloping ascent, making the line  $b_2$ . This slow curved ascent is due to the gradual sinking in of the tactile disk into the inelastic tissue. When the weight is removed at  $y$ , the lever descends along the line  $c_1$  as the tactile disk rises from its depression but soon reaches its lowest point and descends no further, on account of the depression formed in the inelastic tissue remaining ("pitting"). The line  $c_2$  remains, therefore, some distance from the original base line, this difference representing the loss of elasticity. Curve 3 represents the opposite condition from elasticity, namely, plasticity. At the point  $x$ , the weight is added, and the lever ascending slowly makes the line  $b$ . At the point  $y$ , the weight is removed but on account of the plasticity, the tactile disk remaining in the

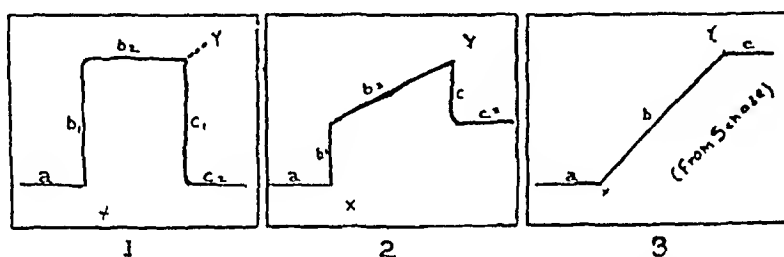


Fig 2—Diagrammatic representation of curves that may be theoretically obtained by the elastometer. Full description given in the text.

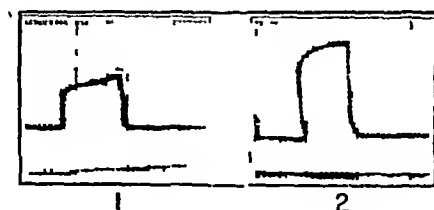


Fig 3—Height of curve varying with amount of subcutaneous tissues.

depression formed, the lever does not descend but continues along the line  $c$ . Not only is the degree of elasticity expressed by the difference between the line  $c_2$  and the original base line, but by the character of the ascending and descending curves.

In our early work with the instrument, following Schade, we expressed readings in percentages. We have found that variation in percentages may result from relative changes in the various tactile disks on the skin surface, causing a difference in the height of a curve. Rearrangement of the tactile disks on the skin surface may place the curve-forming disk on a part having a greater amount of subcutaneous tissue, which would give a greater height to the ascent curve. Hereby it may occur that with the change in the height of the curve there may be associated a change in the elasticity expressed in percentage. This becomes a very important yet uncontrollable factor in the comparison of readings taken from two separate parts of the body or on two separate individuals. Thus, a reading on the leg would give a higher curve than one on the wrist, and it may happen that the percentage loss of elasticity on the leg is greater than on the wrist, despite the fact that there is a palpable edema on the wrist and not on the leg.

Figure 3 illustrates a difference in the height of the curves depending on a rearrangement of tactile disks. In this case there is no loss of elasticity. A large amount of subcutaneous adipose tissue may give abnormal curves not dependent on elasticity loss.

The curves obtained by the elastometer in individuals with normal elasticity (Fig 4) show a rapid perpendicular ascent, an almost horizontal upper line, and a perpendicular descent line, the base of the last line being on a level with the original base line or becoming so within a minute.

Following Schade, we have taken a one minute interval as the standard time in which the curve is formed, and allow one minute after the removal of the weight for the return to the base line. When on taking a reading at a certain point a faultless curve is not obtained, due to the patient's movements or other causes, the tactile disks should be moved, since depression in the skin formed by immediate previous readings may affect the character of subsequent readings obtained from that part. Figure 5 shows three successive readings taken on the same point without moving the tactile disks. The first curve shows a definite loss of elasticity, the second and third curves show less loss, taking the preceding return line as the base line.

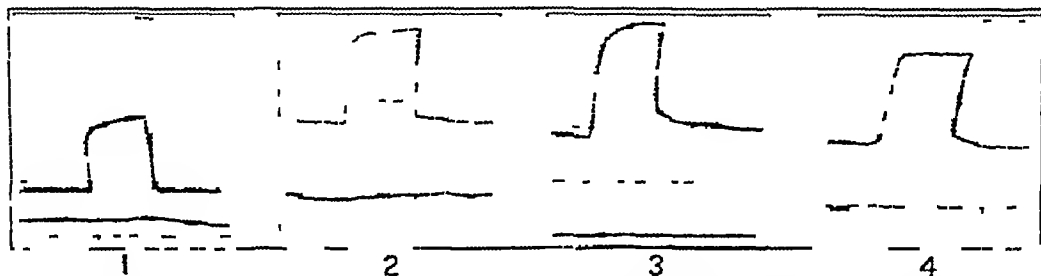


Fig 4—Normal elasticity curves, readings taken at wrist. Curve 1, T H, neurasthenia, Curve 2, N F, chronic endocarditis, Curve 3, F O, chronic endocarditis, Curve 4, S R, contracture of foot.



Fig 5—Successive readings taken on same point without rearranging disks. Wrist readings.

#### OBSERVATIONS

In edema resulting from general causes, such as that associated with cardiac insufficiency or nephritis, while, by ordinary palpation, this edema may seem to confine itself to a definite locality such as the face or extremities, the elastometer will usually show a more generalized loss of elasticity. Figure 6 shows readings taken on the wrists of patients who showed no palpable edema at the wrist, but had palpable edema at some other part of the body. With a severe edema present in any part of the body, readings taken at the wrist will generally show slight or moderate losses of elasticity, which will usually persist even after the palpable edema in the distant part has disappeared (Fig 7).



Curve 1 is a reading taken on the forehead of a patient with a chronic endocarditis, who had a postscarlatinal nephritis at the time of the reading. The face showed a marked edema, which was not only palpable but visible. The urinalysis at this time showed a large amount of albumin, hyaline and granular casts. The reading in the curve is the characteristic one of a severe edema, the sloping gradual ascent and the deficient return to the base line on removal of the weight. Curve 2 was taken nearly a month later when the patient exhibited no palpable edema on any part of the body and the urine was free from casts and albumin. Despite the entire disappearance of palpable edema, the wrist shows a slight loss of elasticity.

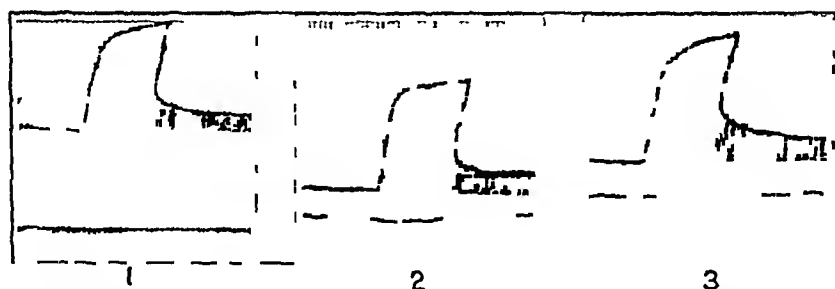


Fig 6—Edema demonstrated by elastometer though not palpable when reading is taken. Curve 1, hydrothorax, no palpable edema any part of body. Reading at wrist. Curve 2, nephritis, chronic, edema palpable in lower extremities. Reading at wrist. Curve 3, endocarditis, mitral, chronic. Moderate edema of lower extremities. Reading at wrist.

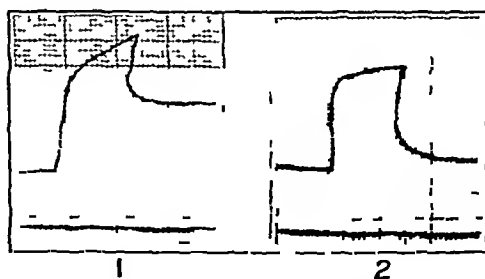


Fig 7—A. K., Curve 1. Forehead. Palpable and visible edema (Dec 11, 1914). Curve 2. Wrist. No palpable edema over any part of body (Jan 4, 1915).

In patients with nephritis we have observed persistent elasticity loss even after the disappearance of all other symptoms. Curve 2, Figure 8, shows a reading taken on a patient with chronic nephritis. This patient had previously presented symptoms of a uremic character, at which time there was a generalized palpable edema, ascites, excretion of urine for a few days almost approaching anuria, phenolsulphonephthalein excretion 15 per cent in two hours. The patient slowly improved and at the time the reading was taken showed no evidence of any trouble except the faintest trace of albumin and the elasticity

loss exhibited in the curve. The patient was discharged, but since then has been readmitted with palpable edema and the usual urinary findings of a chronic nephritis.

In one other similar case of nephritis, a gradually diminishing but persistent elasticity loss was succeeded by a recurrence of the other symptoms which had entirely disappeared. In these cases the elastometric readings served as a helpful gauge of the progress of the disease.

It is probable that with the improvement of the instrument and the technic of its use, such readings will assume important clinical value.



Fig 8—Curve 1, J T , Curve 2, A J , Curve 3, W S , Curve 4, S G

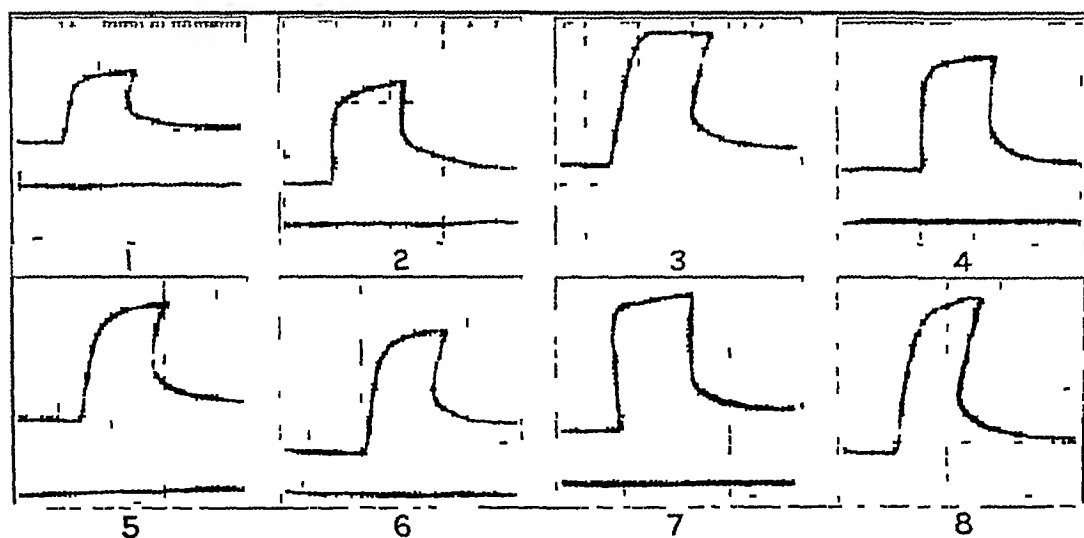


Fig 9—Upper line readings taken on right wrist, lower line readings taken on left wrist. Left to right dated December 6, December 9, December 14, December 26

The manifestation of palpable edema in chronic endocarditis has usually been associated in our minds with serious disturbances of cardiac functions. With the elastometer, slight changes in elasticity are demonstrable in numerous cases of endocarditis without other evidence of decompensation. Curve 1, Figure 8, is a reading obtained on a patient with a mitral endocarditis. This patient was admitted to The Children's Memorial Hospital following a first attack of mitral endocarditis. On admission the patient had painful joints, and the exam-

ination of the heart showed the presence of a soft systolic apical murmur transmitted toward the axilla. At the time the reading was taken there were no subjective or objective signs of a break in compensation. The heart action was regular and strong. The mitral murmur was present as on admission. The patient felt well, and appeared normal. The reading taken at the wrist, however, shows a slight loss of elasticity. Curve 4, Figure 8, is a reading taken on a patient with chronic mitral and aortic endocarditis who at no time showed any palpable edema. Urinalysis was negative. The reading taken at the wrist shows a slight loss of elasticity. Curve 3, Figure 8, illustrates well the known

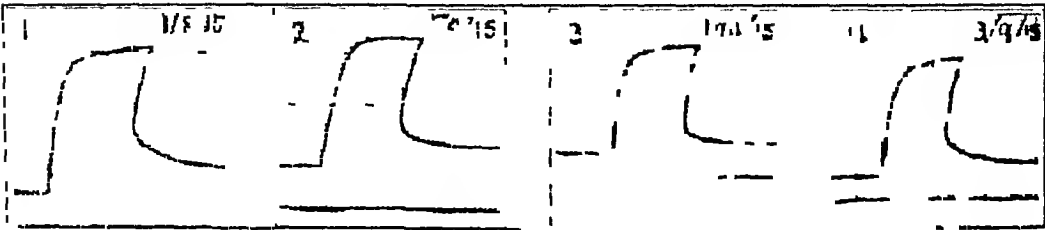


Fig 10—A R, endocarditis, mitral, chronic

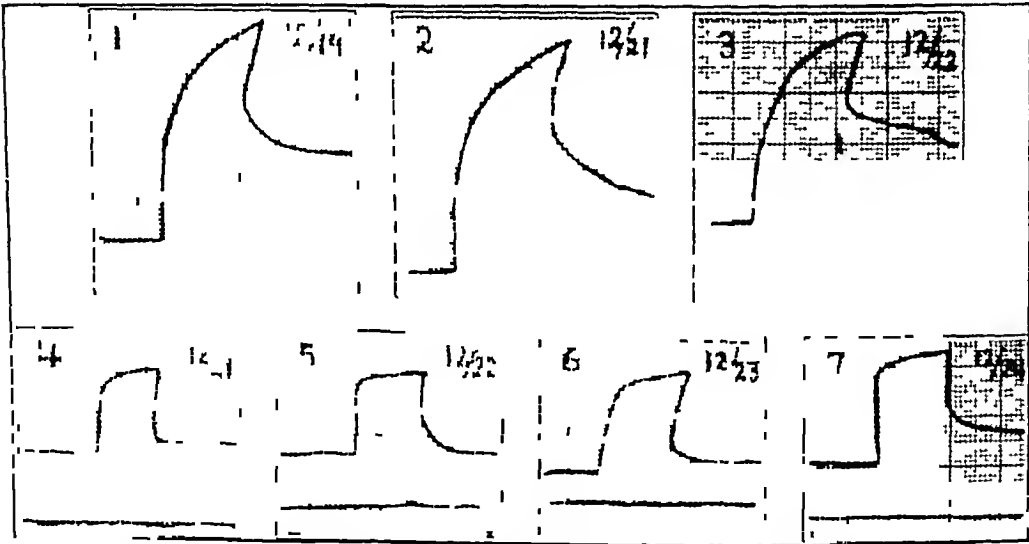


Fig 11—Upper row above malleolus Lower row at wrist

occurrence of edema in anemia. The patient had been in the hospital on several occasions for hemophilia. At the time the reading was taken the patient was in the hospital on account of subcutaneous hemorrhages following injury. Blood examination showed the following

Red cell count	3,980,000
White cell count	6,600
Hemoglobin (Sahli)	31 per cent

The red cells show moderate achromia and quite a bit of anisocytosis. The elastometric reading taken on the wrist shows definite loss of elasticity though the edema is not palpable.

Figure 9 shows readings taken in a case of hydrothorax with general reduced tissue turgor and palpable edema over the chest. This patient was admitted to The Children's Memorial Hospital Dec 5, 1914. The Roentgen-ray examination corroborated the diagnosis of hydrothorax. Heart and urine were normal. Von Pirquet reaction was positive.

Dec 6, 1914—Elastometric reading on both wrists show a decided loss of elasticity. Curve 1, Figure 9.

Dec 9, 1914—Tissue turgor somewhat improved. The elastometric reading shows little change. Curve 2, Figure 9.

Dec 14, 1914—Very slight palpable edema of lower extremities. Elastometric reading, Curve 3, Figure 9. (Little change.)

December 19, 1914—Thoracentesis done, 6 ounces greenish-yellow fluid removed. Cultures negative.

Dec 26, 1914—No palpable edema. Curve 4, Figure 9. Turgor much improved.

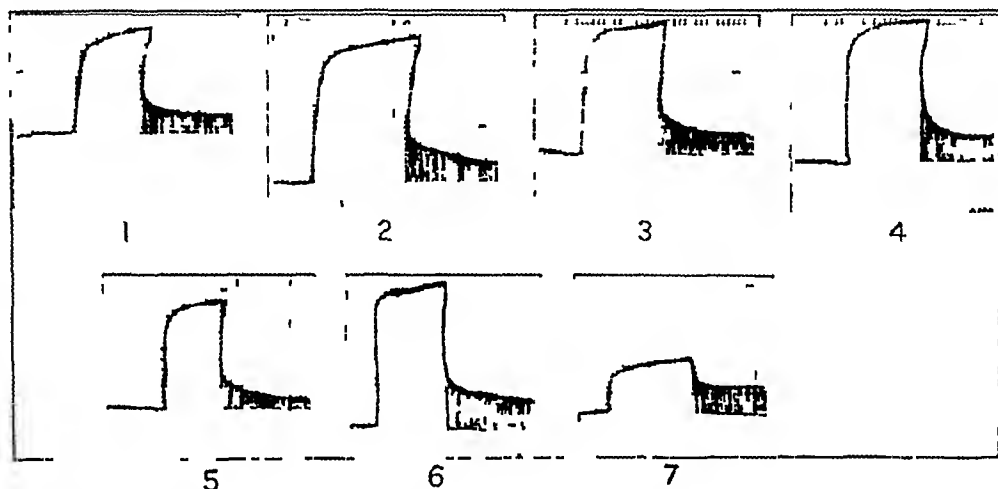


Fig 12—Curve 1, P W, lobar pneumonia, 21 per cent loss, Curve 2, G R, pulmonary tuberculosis, 15 per cent loss, Curve 3, E H, nephritis, 12 per cent loss, Curve 4, J H, lobar pneumonia, 20 per cent loss, Curve 5, F D, unknown infection, 7 per cent loss, Curve 6, T C, pericarditis, 19 per cent loss, Curve 7, L N, miliary tuberculosis, 44 per cent loss.

With improvement of the tissue turgor, with diminution of the fluid in the pleural cavity, with decline of the temperature curve, the elastometric readings show a gradual return to normal. The upper line of readings was taken on the right wrist, the lower line on the left wrist, at neither of which parts was there at any time any palpable edema.

We have further data on cases of pneumonia, to be published later, indicating an interrelationship between fever and edema.

Figure 10 is a series of readings taken on a patient with chronic mitral endocarditis. This patient was admitted to The Children's Memorial Hospital, Dec 5, 1914, at which time there was no palpable edema.

Jan 7, 1915—Child appears much worse. Face puffy. Edema palpable over sacrum and very slightly over tibiae. Breathing labored and noisy, patient restless, and has a cyanotic pallor.

Jan 8, 1915—Elastometric reading at wrist shows a decided loss of elasticity

Jan 9, 1915—Elastometric reading shows similar findings

Jan 12, 1915—Child somewhat better, breathing is quieter Following restriction of fluids and active catharsis, edema of face has diminished Feet and sacrum still show slight palpable edema

Jan 14, 1915—Elastometric reading shows less edema than on January 9

March 9, 1915—No palpable edema Patient comfortable Elastometric reading shows still some loss of elasticity persisting

Here, again, the elastometer not only recorded fluctuations in the amount of edema, but showed the presence of edema after its subjective perception was absent

Figure 11 shows a series of readings taken on a patient with marked palpable edema of the feet from an unknown cause (cirrhosis of liver?) The three upper readings, showing the usual curve of a severe edema, were taken just above the malleolus The lower line of readings taken on the wrist show a gradually increasing elasticity loss, Curves 4 and 5 show very slight evidence of edema, but Curves 6 and 7 show quite distinct losses of elasticity At no time did the wrist show any palpable edema

Figure 12 illustrates the mathematical expression of edema The shaded portion represents the deficient return of the base line Each small square on the figure represents a millimeter The percentage loss of elasticity is obtained by dividing the number of millimeters between the return line and base line (one minute after removal of the weight) by the height of the curve expressed in millimeters

#### DISCUSSION

It is here seen that by means of the elastometer, the study of edema becomes a more accurate one Though, with the present instrument, the expression of edema in mathematical terms is not deemed advisable, the character of the curves, together with the deficiency of return to the base line permit of an approximate estimation of the intensity of an edema

Furthermore, the instrument makes possible the recognition of slight degrees of edema which heretofore could not be detected Persistent evidence of elasticity loss, despite the disappearance of other signs in patients with nephritis or endocarditis, indicates the advisability of more prolonged observation of cases of this character

# THE URIC ACID SOLVENT POWER OF URINE AFTER ADMINISTRATION OF PIPERAZIN, LYSIDIN, LITHIUM CARBONATE AND OTHER ALKALIES \*

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PORTLAND, ORE

In a recent paper<sup>1</sup> I reported the results of an investigation of the uric acid dissolving power of hexamethylenamin. The mode of action of that drug is quite different from that of the rest of those substances which have been classed as "uric acid solvents." The latter, if they act at all as solvents, do so by virtue of being basic substances. The purpose of this paper is to report an investigation of the solvent power of the most important members of this class.

The organic compounds piperazin and lysidin are amine derivatives, and the nitrogen of their molecules imparts to these substances a basic character so that they combine with acids. They are supposed to form salts with uric acid which are very soluble. And it is true that in aqueous solution they dissolve a very large amount of uric acid (see Table 10).

Lithium carbonate and sodium bicarbonate are supposed to act as alkalies toward uric acid, forming lithium and sodium urates which are quite soluble. In aqueous solution they certainly do cause a considerable quantity of uric acid to go into solution (Table 10).

Furthermore, each of these four solvents when added to urine or phosphate mixture, causes the urine to take up much more uric acid than it could dissolve without the addition of the drug (Tables 8 and 9). It remains to be determined, therefore, whether after administration of these drugs the urine acquires a greater uric acid solvent power than normal urines of similar character (as regards concentration and acidity) would have, in other words, whether the drug is excreted in such form and concentration as to show demonstrable uric acid solvent action due to the drug itself. This is what we have tried to determine.

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\* From the Department of Biochemistry, Medical School, University of Oregon

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1 Haskins, H. D. THE ARCHIVES INT. MED., 1915, xvi, 1055

TABLE 1—URINES AFTER TAKING A DRUG—  
LESS DILUTE URINLS AFTER PIPERAZIN

Acidity	Dosage Gm	Time Hours	Piper Test	Uric Acid Content Mg	Total Uric Acid Mg	Uric Acid Dissolved Mg
74*	2×2	0-2	+	71 36	612 48	541 12
73*	2	2-4	Trace	90 36	695 32	604 96
73*	2	0-2		43 63	484 94	441 31
72*	2	0-1½	+	22 80	367 90	345 10
69	2	0-3½	+	62 24	664 92	602 68
69	2	2-3	+	16 64	309 24	292 60
69	2	0-2	+	75 92	288 72	212 80
69	2	0-3	+	80 24	203 60	123 36
685	2	3-4	+	12 08	214 24	202 16
675	2	3-4¼		18 87	221 53	202 66
62	2	0-2¼	+	79 72	500 00	420 28
60	2	0-5½	+	63 00	115 44	52 44
58	2	0-2	+	30 32	116 96	86 64

TABLE 2—  
DILUTE URINLS AFTER PIPERAZIN

69	1	0 - ½		9 20	94 00	84 80
655	1	½-1¾		8 40	48 20	39 80
65	2	4 -5½		23 20	82 00	58 80
65	1×2	1 -1½		9 20	61 20	52 00
65	2	1½-2		10 00	60 40	50 40
645	1×4	0 - ½		7 60	19 60	12 00
64	1×4	¾-1¾		9 20	44 40	35 20
635	1	0 -1		10 44	47 44	37 00
63	1×4	1½-2		9 20	43 60	34 40
625	1×3	¼-¾		8 40	18 00	9 60
61	2	¾-4¼		10 00	52 80	42 80
61	2	½-1½		9 20	26 00	16 80
60	2	0 -2½		7 52	55 40	47 88
60	2	2 -2¾		8 40	25 20	16 80

TABLE 3—  
LESS DILUTE URINES AFTER LYSIDIN

71	2×2	½-2½		38 00	178 00	140 00
71	2×2	5 -6		112 40	200 00	87 60
61	2	0 -1		31 60	68 40	36 80
60	2×2	2½-4		22 00	51 60	29 60
585	2	0 -3		56 92	130 64	73 72
585	2×2	0 - ½		52 00	71 60	19 60
58	2	0 -4½		63 76	109 36	45 60
58	2	0 -2¼		78 96	101 76	22 80

—CONTROLS URINES WITHOUT THE DRUG

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg.	Total Uric Acid Mg.	Uric Acid Content Mg	Acidity	Remarks
283 14	296 94	13 80	76*	* NaHCO <sub>3</sub> adminis- tered
350 00	446 55	96 55	73*	
255 75	360 75	105 00	73*	
223 50	279 00	55 50	72*	
198 40	247 60	49 20	70	
159 20	282 00	122 80	69	
158 84	230 20	71 36	69	
102 76	137 26	34 50	69	
154 40	216 40	62 00	68	
148 00	198 00	50 00	67	
31 20	75 60	44 40	64	
15 20	72 40	57 20	63	
8 80	34 00	25 20	61	
40 56	76 20	35 64	59†	
				† A very exceptional control

—TABLE 2—(Continued)

DILUTE NORMAL URINES

141 75	150 08	8 33	69	The drug seems to be- gin to be excreted very soon and to be present in the urine in appreciable amount for at least four hours The urines in this table are too dilute to give tests for the drug
111 75	120 00	8 25	69	
47 95	62 91	14 96	655	
63 92	76 16	12 24	65	
49 58	59 28	9 70	65	
50 80	66 00	15 20	65	
51 48	59 04	7 56	645	
31 20	38 80	7 60	64	
22 94	30 42	7 48	635	
33 75	41 25	7 50	63	
19 20	31 60	12 40	63	
19 50	27 06	7 56	625	
37 92	52 33	14 41	60	
12 00	22 00	10 00	60	

—TABLE 3—(Continued)

LESS DILUTE CONTROL URINES

172 00	244 40	72 40	71	* A very exceptional control
135 42	185 82	50 40	71	
8 80	34 00	25 20	61	
40 56	76 20	35 64	59*	



The citrates and acetates of sodium and potassium are converted in the body into bicarbonate, so that their effect on the urine should be the same as that of sodium bicarbonate. It seemed advisable, however, to test sodium citrate experimentally so as to make sure of the effectiveness of this class of salts.

While conducting a research on atophan, its uric acid solvent power was determined incidentally, although there was no reason to suppose that it belonged to the class of uric acid solvents. I take this occasion to report the results. The urines from eight persons (twenty-four-hour samples) were of low enough acidity to lead to the expectation that they might dissolve extra uric acid. Their content of uric acid ranged from 80 to 132 mg in 100 c c. Only one of the urines took up any uric acid, however, this had an acidity of 6.8 and dissolved 46 mg, which was less than a normal urine of that acidity would be expected to dissolve. The indications are, therefore, that atophan may interfere with the solvent action of the urine.

The urines reported in the tables were all from normal individuals. They are not as numerous as we had hoped to secure, since few persons were willing to take these drugs.<sup>2</sup> Hospital urines were not obtainable.

The methods used in the present investigation were identical with those reported in the paper on hexamethylenamin. The results of our work are given in the tables where comparison is made of the uric acid dissolved by the drug urines with that dissolved by normal urines of similar acidity and concentration. In interpreting our results we take it for granted that the drug urine must show distinctly greater solvent power than the control normal urines, in order to permit us to argue that the drug plays any part in the solvent action.

The figures for uric acid are given as milligrams in 100 c c of urine. "Uric acid content" means the amount present in the urine as passed. "Total uric acid" means the amount present in the filtrate after shaking the urine with pure uric acid for twenty minutes at 37 C. The difference between these two is the "uric acid dissolved." This last is the index of the solvent power of the urine.

In the cases in which more than one dose of the drug was taken, the time interval for secretion of the urine was calculated from the time of taking the last dose.

In Table 9 the acidity figures are those of the phosphate mixture ( $\text{NaH}_2\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$  mixed as in urine) before any drug was added. The drugs rendered the solutions alkaline. In Table 10, on the other hand, the acidity figures are those of the solutions of the drugs.

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2 The author wishes to express his gratitude to those, students and others, who did assist him so materially in this respect, foremost among whom were Dr. P. J. Hanzlik, Dr. R. J. Collins and C. J. Friedman. The assistance of Mr. Friedman in all the work of the research was invaluable.

In connection with Table 8, attention must be called to the fact that the urines of the same acidity are not different urines but portions of the same urine. The effect of the drugs in changing the reaction of the urine is of sufficient interest to report (Table 11)

#### COMMENT ON THE TABLES

In the case of the dilute urines (Tables 2 and 4) after taking piperazin and lysidin, the results are not significant, possibly because dilution of the drug reduces its effect so that no conclusion as to solvent action can be drawn

In Table 1 are found some very striking results. The first, second, third and fifth urines dissolved an excessive amount of uric acid, much beyond our expectations of what could be dissolved by any substance excreted into the urine. The sixth urine shows a high result for a urine of an acidity 6.9. Even though the solvent action be due in part to the bicarbonate taken also, yet there can be no doubt whatever that the piperazin has been excreted in sufficient quantity to exert a very decided solvent action.

It is true that the 2 gm. doses are extratherapeutic, but we see no reason why the maximum therapeutic dose should not have a distinct effect, at least when the urine is not dilute and is not acid in reaction.

In the case of lysidin, the two alkaline urines, the first two of Table 3, do not show sufficient solvent action to be able to attribute any of it to the drug. The dosage being equal to the maximum therapeutic dose, we expected to secure evidence of some solvent action if there was enough action to be worth considering.

We knew of no way of determining whether lysidin is excreted either unchanged or as a derivative which could be effective as a uric acid solvent.

The results in Table 8 indicate that lysidin ought to be an effective solvent provided it is excreted unchanged and rapidly enough to give a proper concentration in the urine. We may also add the qualifying statements as in the case of piperazin, that the urine should not be dilute nor acid in reaction.

We would not expect that the basic compounds, piperazin and lysidin, could show any solvent action in acid urines, yet several surprising results are to be found in Tables 1 and 3. The eleventh urine in Table 1, of 6.2 acidity, took up 420 mg. of uric acid, a result which is quite remarkable. Several more acid urines showed distinct solvent power beyond what we have ever secured with normal urines of those acidities. These are the last urine of Table 1 (5.8 acidity, 86 mg. dissolved), and the fifth (5.85 acidity, 73 mg. dissolved) and seventh (5.8 acidity, 45 mg. dissolved) urines of Table 3. Our experience with normal urines has led us to expect no solvent action whatever if the

TABLE 4—

## DILUTE URINES AFTER LYSIDIN

Acidity	Dosage Gm	Time Hours	Uric Acid Content Mg	Total Uric Acid Mg	Uric Acid Dissolved Mg
6.75	2×2	0 - ¾	14.00	121.20	107.20
6.35	1×4	¾-1½	8.40	52.40	44.00
6.35	1×4	0 - ¾	7.60	43.60	36.00
6.3	2×2	3¼-5	10.80	42.80	32.00
6.2	1×4	1½-2½	8.40	62.00	53.60
6.1	1×2	0 - ¼	7.60	58.00	50.40
6.0	1	0 - ¾	10.80	59.60	48.80
6.0	1×4	2½-4	9.20	43.60	34.40
6.0	2	2 - 3	9.20	26.00	16.80

TABLE 5—URINES AFTER ADMINISTRATION OF ALKALIES—  
LESS DILUTE URINES AFTER LITHIUM CARBONATE

Acidity	Dosage Gm	Drug	Uric Acid Content Mg	Total Uric Acid Mg	Uric Acid Dissolved Mg
7.0	†	Li <sub>2</sub> CO <sub>3</sub>	50.80	176.40	125.60
6.85	†	Li <sub>2</sub> CO <sub>3</sub>	29.20	142.00	112.80

TABLE 6—

## DILUTE URINES AFTER LITHIUM CARBONATE

7.6	10	Li <sub>2</sub> CO <sub>3</sub>	15.40	244.34	228.94
7.2	10	Li <sub>2</sub> CO <sub>3</sub>	19.33	421.52	402.19
7.15	0.5×2	Li <sub>2</sub> CO <sub>3</sub>	12.40	114.80	102.40
7.0	0.5×2	Li <sub>2</sub> CO <sub>3</sub>	18.40	136.50	118.10
6.95	†	Li <sub>2</sub> CO <sub>3</sub>	12.40	214.80	202.40
6.95	†	Li <sub>2</sub> CO <sub>3</sub>	13.20	159.60	146.40
6.95	†	Li <sub>2</sub> CO <sub>3</sub>	11.60	145.20	133.60
6.9	0.5×2	Li <sub>2</sub> CO <sub>3</sub>	9.20	142.00	132.80

TABLE 7—

## LESS DILUTE URINES AFTER SODIUM SALTS

7.6	4	NaHCO <sub>3</sub>	13.80	296.94	283.14
7.3	4	NaHCO <sub>3</sub>	96.55	446.55	350.00
7.3	4	NaHCO <sub>3</sub>	105.00	360.75	255.75
7.3	3	Sod citrate	70.50	283.87	213.37
7.3	3	Sod citrate	129.24	313.85	184.61
7.25	3	Sod citrate	56.00	227.20	171.20
7.25	3	Sod citrate	72.00	222.26	150.26
7.2	2	NaHCO <sub>3</sub>	55.50	279.00	223.50
7.2	3	Sod citrate	52.02	218.94	166.92
7.15	3	Sod citrate	27.00	210.41	183.41
7.1	2	Sod citrate	30.57	197.88	167.31

ABLE 4—(Continued)

DILUTE NORMAL URINES

Uric Acid Dissolved Mg	Total Uric Acid Mg	Uric Acid Content Mg	Acidity	Remarks
83 00	91 25	8 25	6 75	These drug urines are too dilute doubtless to show solvent ac- tion due to the drug
48 75	68 40	19 65	6 4	
22 94	30 42	7 48	6 35	
33 75	41 25	7 50	6 3	
7 20	22 80	15 60	6 2	
37 92	52 33	14 41	6 0	
12 00	22 00	10 00	6 0	
14 82	25 50	10 68	5 95	

—CONTROL URINES

LESS DILUTE CONTROL URINES

Uric Acid Dissolved Mg	Total Uric Acid Mg	Uric Acid Content Mg	Acidity	Remarks
187 60	240 00	52 40	7 0	† 15 gm in 1 L water taken in one day
131 20	174 00	42 80	6 8	

—TABLE 6—(Continued)

DILUTE CONTROL URINES

144 75	154 50	9 75	7 3	* Urines containing bi- carbonate
157 29	172 25	14 96	7 1	
283 14	296 94	13 80	7 6*	
350 00	446 55	96 55	7 3*	
255 75	360 75	105 00	7 3*	
118 40	138 80	20 40	7 0	† (As above)
105 66	122 16	16 50	6 95	
141 75	150 08	8 33	6 9	
130 07	139 06	8 99	6 9	
111 75	120 00	8 25	6 9	

—TABLE 7—(Continued)

LESS DILUTE CONTROL URINES

				All of these urines showed presence of bicarbonate
188 50	234 34	45 84	7 2	
188 16	250 08	61 92	7 2	
182 04	238 36	56 32	7 2	
172 00	244 40	72 40	7 1	
162 40	207 60	45 20	7 0	

acidity was as great as 58 or 59 and the urine was not dilute. The control urine given in Tables 1 and 3, 59 acidity 40 mg dissolved, stands out as the sole (and unexplained) exception.

We have no explanation to offer as to how it is possible for piperazin and lysidin to show uric acid solvent power in these acid urines, but we can not avoid the conclusion that these results are very striking evidence that such solvent power exists.

Although we admit that lysidin may impart to the urine solvent properties due to the drug, we do not consider it practical to use it, because of the enormous dosage that would be necessary in order to secure pronounced effects comparable to the effect of piperazin.

Piperazin, however, would seem to be especially suitable for securing an intense uric acid solvent action, provided very large doses are given for a short time, together with sodium citrate or bicarbonate (so that the urine is alkaline).

The acid urines which we obtained after administration of alkalis are not reported in Tables 5, 6 and 7 for the following reason. The fact that the urine remains acid shows that the alkali has been neutralized in the body and is being excreted in the form of a salt. The only chance for the alkali increasing the solvent power of the urine in such a case would be by causing an increase in the amount of monohydrogen phosphate, and such increase would have but a moderate effect, resulting in no greater uric acid solvent power than could be duplicated by normal urines.

A massive uric acid solvent action, however, is shown by some alkaline urines, probably because they bring about colloidal solution of the uric acid. Schade and Boden<sup>3</sup> secured colloidal solutions of uric acid by using aqueous solutions of alkalis. Such an action is shown apparently by the second urine of Table 6 (72 acidity, 402 mg dissolved). This is the only significant result with lithium carbonate. The solvent action is greater than we have secured with urines rendered alkaline by giving sodium bicarbonate or citrate. Having secured toxic symptoms in two persons taking lithium, we did not attempt to use very large doses nor to give it to many individuals. We are certain that lithium carbonate is not effective in smaller doses than those used by us. There is no real reason for giving it, since it is much safer to use the sodium salts.

Table 7 shows that the sodium salts give a sufficiently marked and a very reliable uric acid solvent action, whenever they have rendered the urine at least faintly alkaline. We can not see why any other drugs should ever be chosen in preference to them.

3 Schade and Boden. *Ztschr f physiol Chem*, 1913, *IXXXIII*, 347

TABLE 8—EFFECT OF DRUGS ADDED TO URINE

Acidity	Drug Added	Per Cent of Drug	Control Uric Acid Dissolved (No Drug) Mg	Uric Acid Dissolved (After Drug Was Added) Mg	Excess of Uric Acid Dissolved Due to the Added Drug Mg
50	Piperazin	0.680	0.00	233.32	233.32
624	Piperazin	0.125	19.50	99.84	80.34
60	Piperazin	0.132	27.30	103.74	76.44
58	Piperazin	0.085	19.00	47.12	28.12
58	Piperazin	0.142	19.00	78.28	59.28
58	Piperazin	0.170	19.00	85.12	66.12
58	Piperazin	0.200	19.00	103.36	84.36
58	Piperazin	0.230	19.00	120.08	101.08
58	Piperazin	0.260	19.00	152.76	133.76
60	Lysidin	0.050	27.30	60.84	33.54
60	Lysidin	0.100	27.30	99.06	71.76
60	Lysidin	0.200	27.30	186.42	159.12
50	Lysidin	1.000	0.00	129.96	129.96
50	$\text{Li}_2\text{CO}_3$	0.157	0.00	245.48	245.48
50	$\text{NaHCO}_3$	1.000	0.00	288.80	288.80

TABLE 9—EFFECT OF DRUGS ADDED TO PHOSPHATE SOLUTION

68	Piperazin	0.500	120.00	274.00	154.00
68	Piperazin	1.000	120.00	511.40	391.40
68	$\text{Li}_2\text{CO}_3$	0.168	138.24	340.40	202.16

TABLE 10—EFFECT OF DRUGS ADDED TO WATER

7.25	Piperazin	0.50	8.4	250.80	242.40
	Piperazin	0.65	8.4	541.80	533.40
	Piperazin	1.00	8.4	527.60	519.20
7.4	Lysidin	1.00	8.4	455.92	447.52
7.4	$\text{Li}_2\text{CO}_3$	0.16	8.4	503.80	495.40
7.25	$\text{NaHCO}_3$	1.00	8.4	484.80	476.40

TABLE 11—ACIDITY OF THE URINE AS AFFECTED BY DRUGS

Before the Drug	After the Drug	Drug Used	Per Cent
50	7.4	Piperazin	0.68
50	7.1	Lysidin	1.0
50	7.1	$\text{Li}_2\text{CO}_3$	0.157
50	6.8	$\text{NaHCO}_3$	1.0
58	6.0	Piperazin	0.085
58	6.25	Piperazin	0.142
58	6.55	Piperazin	0.17
58	6.85	Piperazin	0.20
58	6.95	Piperazin	0.23
58	7.2	Piperazin	0.26

We called attention in the previous paper to the favorable effect of dilution of the urine. Probably the greatest total solvent action would be secured by combining diuresis from heavy drinking of water with the alkalization of the urine by sodium bicarbonate or citrate.

Whenever normal urine becomes alkaline and it contains a considerable concentration of metal ions as a result of the diet, it will show marked uric acid solvent action, exactly as it would if sodium bicarbonate had been taken and for the same reason. Blatherwick<sup>4</sup> has also observed this fact. We have found that normal alkaline urines always contain bicarbonate as well as the alkaline urines passed after taking sodium citrate or bicarbonate.

#### CONCLUSIONS

1 Piperazin can cause the urine to dissolve more uric acid than it would without the drug, and this effect is most marked if sodium citrate or bicarbonate be also given and if diuresis be avoided.

2 Lysidin can act as a uric acid solvent but is not a practical therapeutic agent because of the large doses required.

3 Lithium carbonate is a uric acid solvent if large enough doses are used, but is unsafe and possesses no advantage over sodium citrate or bicarbonate.

4 Sodium citrate and bicarbonate are reliable and satisfactory uric acid dissolving agents when given in such dosage as to keep the urine alkaline.

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4 Blatherwick, N. R. *THE ARCHIVES INT. MED.*, 1914, xiv, 409.

## SEROLOGIC EXAMINATIONS IN A CASE OF POLYCYTHEMIA \*

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AND

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DETROIT

Recently Lucas<sup>1</sup> in an exhaustive article on erythremia reviewed the literature in a comprehensive manner, adding two new cases to the series. It is apparent that a greater number of cases of polycythemia with chronic cyanosis and with or without splenomegaly are being recognized.

Among the various theories advanced as to the cause of erythremia, the one originally suggested by Rendu and Widal,<sup>2</sup> and later amplified by Osler<sup>3</sup> and Weber,<sup>4</sup> ascribes the changes that take place to unusual erythropoietic activities. Pathological findings have, in a measure, substantiated this explanation, though Saundby and Russell<sup>5</sup> describe normal bone marrow findings in their case. If we are to accept this view of primary excessive formation of red cells in the bone marrow, we have an analogy to myelogenous leukemia, in which the leukoblastic activity dominates the picture. In contrast stands this notable feature of erythremia—the absence of erythroblasts in the circulating blood.

The theory advanced by Belonovsky,<sup>6</sup> that the enlarged spleen elaborates a small amount of hemolysin, enough to excite a hyperactivity of the bone marrow and thereby raise the total number of red cells, as well as the hemoglobin, has also many facts to substantiate it. The occurrence of some cases of idiopathic polycythemia without splenomegaly, as in this instance, leaves us to seek another source of toxin that might have such limited hemolytic activity.

A theory that has had numerous supporters and positive reports to substantiate it has ascribed an increased resistance to hemolysis to

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1 Lucas, Walter S. *THE ARCHIVES INT MED*, 1912, x, 597

2 Rendu and Widal. *Bull Soc med d hôp*, Series 3, 528. Quoted from Osler's article in the *Am Jour Med Sc*, 1903, cxxvi, 187

3 Osler, W. *Bull Johns Hopkins Hosp*, 1903, xix, 91, also, *Am Jour Med Sc*, 1903, cxxvi, 187

4 Weber, F. P. *Proc Roy Soc Med*, London, 1908-09, also, *Internat Clin*, 1905, iv, 47

5 Saundby and Russell. *Lancet*, London, 1902, i, 515

6 Belonovsky. Quoted from Lucas' work. See Note 1



the erythrocytes Guinon, Rist and Simon<sup>7</sup> state that the red cells of their patient resisted hemolysis Parkes Weber<sup>4</sup> reports one case with the resistance to hemolysis about normal

This patient presented the opportunity for a careful serologic study This was undertaken with the view of determining the following questions

- 1 The resistance of polycythemic cells to hemolysis
- 2 The possible presence of antihemolysin or anticomplementary substances
- 3 The presence of complement in the polycythemic serum
- 4 A comparison of complements from the serum of known normal individuals and the polycythemic serum
- 5 The fragility of the polycythemic cells

The patient on whom this study was made presented himself for examination in September, 1912, and has been under almost constant supervision since Like several previously reported cases this man was a Russian Jew, an interesting fact perhaps in the etiology This patient's blood count on the first examination was hemoglobin, 123 per cent, Sahlb Red blood cells, 7,920,000, white blood cells, 6,900 Differential counts showed nothing abnormal No nucleated forms or myelocytes were seen The urine was normal The patient did not react to tuberculin The Wassermann was negative Heart and lungs were normal and there was no evidence of glandular enlargement The spleen could not be palpated on deep breathing Blood pressure, 140 systolic, 80 diastolic Roentgenograms of the heart and mediastinum negative

One of the first things observed in comparing the polycythemic blood with normal blood is the difference in serum and cellular content Equal quantities of polycythemic and of normal blood were compared It was found that the polycythemic patient's blood yields but one-half the amount of serum that the normal does

PROTOCOL 1

Complement, c c *	Amboceptor, c c †	One Per Cent Suspension Normal Human Cells, c c ‡	Result
0.6	0.5	1	Complete hemolysis
0.5	0.5	1	Complete hemolysis
0.4	0.5	1	Partial hemolysis

\* 10 per cent guinea pig serum

† 1 unit = 0.007 c c Dilute to 0.5 c c

‡ Normal saline to 2.5 c c, incubate at 37.5 C 30 minutes

*Protocol 1*—Preliminary titer showing the amount of 10 per cent guinea-pig complement required to produce complete hemolysis of 1 c c of a 1 per cent suspension of normal human red cells

<sup>7</sup> Guinon, Rist and Simon Bull et mém Soc d hôp de Paris, 1904, xx1, 786

## PROTOCOL 2

Complement, cc *	Amboceptor, cc †	One Per Cent Suspension Polycythemic Cells, cc ‡	Result
0.6	0.5	1	Complete hemolysis
0.55	0.5	1	Complete hemolysis
0.5	0.5	1	Complete hemolysis
0.45	0.5	1	Partial hemolysis
0.4	0.5	1	Partial hemolysis
0.35	0.5	1	Slight hemolysis

\* 10 per cent guinea pig serum

† 1 unit = 0.007 cc Dilute to 0.5 cc

‡ Normal saline to 2.5 cc, incubate at 37.5 C 30 minutes

*Protocol 2*—Using 1 cc of a 1 per cent suspension of polycythemic red blood cells with varying amounts of the complement dilution we find 0.5 cc of complement produces complete hemolysis as in Protocol 1. This shows that the polycythemic cells are not unusually resistant to hemolysis.

## PROTOCOL 3

Complement, cc *	Amboceptor, cc †	Polycythemic Serum, cc ‡	One Per Cent Suspension Polycythemic Cells, cc §	Result
0.6	0.5	0.25	1	Complete hemolysis
0.5	0.5	0.25	1	Complete hemolysis
0.4	0.5	0.25	1	Partial hemolysis

\* 10 per cent guinea pig serum

† 1 unit = 0.007 cc Dilute to 0.5 cc

‡ Double amount required for hemolysis Inactivate at 56 C 30 minutes

§ Normal saline to 2.5 cc, incubate at 37.5 C 30 minutes

*Protocol 3*—The addition of relatively large amounts of polycythemic serum which had been inactivated at 56 C for one-half hour did not inhibit the hemolysis of the polycythemic cells.

## PROTOCOL 4

Complement, Polycythemic Serum, cc	Amboceptor, cc *	One Per Cent Suspension Polycythemic Cells, cc †	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis
0.18	0.5	1	Complete hemolysis

\* 1 unit = 0.007 cc Dilute to 0.5 cc

† Normal saline to 2.5 cc Incubate at 37.5 C 30 minutes

## PROTOCOL 5

Complement, Polycythemic Serum, cc	Amboreceptor, cc*	One Per Cent Suspension Normal Human Cells, cc†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis
0.18	0.5	1	Complete hemolysis

\* 1 unit = 0.007 cc Dilute to 0.5 cc

† Saline to 2.5 cc Incubate at 37.5 C 30 minutes

*Protocols 4 and 5*—Comparison of Protocols 4 and 5 shows that equal amounts of normal human and polycythemic red cells require equal amounts of polycythemic serum used as complement to produce complete hemolysis

## PROTOCOL 6

Case A, Complement, Normal Serum, cc	Amboreceptor cc*	One Per Cent Suspension Normal Cells, cc†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis

\* 1 unit = 0.007 cc Dilute to 0.5 cc

† Saline to 2.5 cc Incubate at 37.5 C 30 minutes

Case A, Complement, Normal Serum, cc†	Amboreceptor, cc*	One Per Cent Suspension Polycythemic Cells, cc†	Result
0.03	0.5	1	No hemolysis
0.06	0.5	1	Partial hemolysis
0.09	0.5	1	Complete hemolysis
0.12	0.5	1	Complete hemolysis

\* 1 unit = 0.007 cc Dilute to 0.5 cc

† Saline to 2.5 cc Incubate at 37.5 C 30 minutes

‡ The above was repeated using serum of four other healthy adults and gave identical results

*Protocol 6*—The serum of healthy normal adults was taken and used as complement for comparison with the polycythemic serum. The complement contained in normal serum hemolyzed normal red cells and polycythemic cells in the same quantities and at the same rate as did the complement contained in the polycythemic serum.

## PROTOCOL 7

Per cent saline solution*	0.1	0.2	0.3	0.4	0.5	0.6		4	5	6	7	7.5	8	9	10
Complete hemolysis	+	+	+									±	±	+	+
Slight hemolysis				+	±				±	+	+				
No hemolysis						+	++	+							

\* The above results were obtained using polycythemic and normal red blood cells

In all the hemolytic experiments a 1 per cent suspension of washed corpuscles taken from a normal healthy adult was used. The quantity used throughout all the work was 1 c c. The normal red cells and the polycythemic cells were centrifugalized at the same speed and for equal periods of time, thereby making certain that both suspensions were of equal strength. The amboceptor unit was 0.007 c c diluted so that 0.5 c c of the dilution was equal to one unit.

## FRAGILITY EXPERIMENTS

For the purpose of determining whether or not the red blood cells of the polycythemic patient were more or less resistant than normal individual's cells to hypertonic and hypotonic saline solution, the following tests were carried out. Blood from the polycythemic and normal individual was removed from the median basilic vein and mixed with an equal volume of 2 per cent citrate solution. Two drops of each were then placed in the saline solutions of varying dilutions with results as indicated in Protocol 7. It is evident from this test that the cells of the polycythemic patient are neither more nor less fragile than the cells of the control individual.

## CONCLUSIONS

1 Quantitatively the polycythemic patient has approximately one-half the amount of complement that a normal adult has.

2 Qualitatively the complements from the polycythemic patient and from normal adults are of equal potency.

3 The polycythemic serum contains no anticomplementary bodies.

4 The polycythemic red cells are neither more nor less fragile than red cells from normal adults.

5 Polycythemic and normal red cells are equally resistant to hemolysis.

# ON THE TOXICITY OF VARIOUS COMMERCIAL PREPARATIONS OF EMETIN HYDROCHLORID<sup>1</sup>

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In view of the widespread use of emetin hydrochlorid in the treatment of amebic dysentery and of pyorrhea alveolaris, more precise knowledge of the toxicity of the commercial preparations employed is highly desirable. The following case reports forcibly emphasize this fact.

CASE 1—I B (Med No 33209), white, male, aged 56, a native of Baltimore, was admitted to the surgical service Oct 12, 1914, complaining of an "ulcerated rectum." Fifteen years previously he had had a chancre, followed by a secondary eruption. For the past six years there had been alternating periods of diarrhea and constipation, with blood in the stools at times.

*Examination*—On examination, there was found slight enlargement of the heart to the left, a soft systolic murmur at the apex and some impairment of the percussion note over the manubrium. The systolic pressure was 150 mm Hg, diastolic, 70. The urine was negative. The blood showed red blood corpuscles, 5,720,000, white blood corpuscles, 7,350, hemoglobin (Sahli), 92 per cent. The differential count was normal. The Wassermann reaction was positive. Actively motile amebas were found in the stool, and October 20 the patient was transferred to the medical service with a diagnosis of lues and amebic dysentery.

At this time the stools contained a few pus cells and a little mucus, but repeated examinations revealed no amebas. Sigmoidoscopic examination showed no ulceration or bleeding points, 10 cm from the anus there were two small scars, probably of healed erosions. There was a considerable number of small internal hemorrhoids.

During the first three weeks of his stay in the hospital the patient was having only one or two stools daily. November 5, however, diarrhea developed, on the fifteenth he had eleven bowel movements. No amebas were found.

*Treatment and Course*—November 17, subcutaneous injections of emetin hydrochlorid were begun. Three times a day, from the seventeenth to the twenty-fifth, inclusive, the patient received  $\frac{1}{2}$  grain, on the twenty-sixth and twenty-seventh,  $\frac{1}{3}$  grain, and from November 28 to December 5, inclusive,  $\frac{1}{2}$  grain. A few days after beginning the emetin treatment the number of stools became less. The improvement, however, was only temporary, and on November 26 there were nine, and December 3, eighteen stools in the twenty-four hours. It is noteworthy that December 10, five days after the emetin was discontinued, the diarrhea permanently ceased.

\* Submitted for publication Nov 22, 1915.

\* From the Medical Clinic of the Johns Hopkins Hospital.

\* Eight of the ten original tracings accompanying this article were lost by the engravers. The records appearing in Figures 1, 2, 3, 4, 5 and 8 have been supplied by the authors in this emergency. They do not illustrate the various points brought out in the paper as satisfactorily as did the originals, inasmuch as they represent tracings which had previously been discarded.

December 4, a trace of albumin and a few granular casts appeared in the urine. Gastric analysis showed slight subacidity.

December 8, the phthalein excretion was 18 per cent in two hours. Two days later, the nonprotein nitrogen of the blood was 112 mg per 100 cc, the urea nitrogen, 92 mg. Sellards' test<sup>1</sup> revealed the existence of a high grade acidosis.

The amount of albumin in the urine gradually increased, and December 11, (four days before death) blood appeared. The patient was now slightly dyspneic and complained of nausea and pain in the umbilical region. On the fourteenth, the pulse was weak and rapid, the breathing was of the Cheyne-Stokes variety and coarse râles were heard throughout the chest. The leukocytes had risen to 14,600. The systolic blood pressure, which before had ranged from 150 to 190 mm Hg, had fallen to 95.

December 15, after a period of marked dyspnea, the patient collapsed and died.

The lipase content of the blood obtained at necropsy was 14 per cent.

#### NECROPSY REPORT (DR H N STEVENSON)

*Anatomical Diagnosis*—Syphilitic aortitis, chronic aortic endocarditis, dilatation of the heart, chronic passive congestion of the viscera, arteriosclerosis, chronic indurative colitis, healed tuberculosis of the lung and hilar glands, bronchopneumonia.

*Abstract of Notes*—*Lungs* Diffuse bronchopneumonia. *Liver* Lobulation distinct, irregular patches of congestion, no focal areas of necrosis. Microscopically, the lobulation is well defined, the cells in the periportal zones are large and granular. Cells in central portion of lobules are atrophic and widely separated by congested capillaries. *Spleen* Not enlarged, shows congestion. *Kidneys* Weight, 150 gm each. Cortex about 5 mm in thickness. Striations somewhat irregular and slightly distorted. Glomeruli indistinctly seen as minute, reddish, translucent dots of irregular intensity. Pyramids show slight congestion. Pyramidal striations are regular. Pelvis of each kidney shows some ecchymoses. Microscopically, the arteries show slight intimal thickening. There are a few ill-defined areas in the cortex where there is slight increase in interstitial tissue, and a few areas of round cell infiltration. *Duodenum* Lymphoid elements slightly hyperplastic. No ulceration. *Ileum* Slight flushing of mucosa in its lower portion. *Large Intestine* The lumen is of the usual circumference. The mucosa is everywhere uniform in appearance, there being no erosions or ulcerations. It is of a uniformly pale gray, almost white, color, and the folds of the mucosa are indistinct. The mucosa gives the impression from its consistence of being thicker than normal. The mucous membrane of the rectum is slightly flushed, and microscopically shows marked infiltration by connective tissue and round cells.

**SUMMARY**—A man weighing 153 pounds (69.5 kg) received, daily, subcutaneous injections of emetin hydrochlorid over a period of twenty days. The average daily dose was  $1\frac{1}{2}$  grains (90 mg),<sup>2</sup> or 1.3 mg per kg. *In toto*, he received 29 grains (1.74 gm), or 25 mg per kg.

A previously existing diarrhea was at first apparently somewhat ameliorated, then markedly intensified. On the sixteenth day of treat-

1 Sellards, A. W. Bull. Johns Hopkins Hosp., 1914, xxv, 101.

2 Throughout this paper 1 grain is regarded as the equivalent of 60 milligrams, inasmuch as the dosage of the commercial preparations is calculated on this basis.

ment the patient complained of nausea and abdominal pain. Albuminuria and cylindruria appeared and gradually increased. Finally there was evidence of acute renal insufficiency, with blood in the urine and diminution in the 'phthalein output, along with an increase in the non-protein nitrogen of the blood. There was marked acidosis, as evidenced by the positive Sellards test. Bronchopneumonia and vasomotor collapse terminated the picture.

**CASE 2**—A G E (Med No 33818), a white woman, aged 31, was admitted to the medical service, March 4, 1915, complaining of attacks of nervous sick headache. These attacks, which she had had since childhood, presented all the essential features of migraine. Pigmentation of the arms after exposure to the sun, and occasional attacks of diarrhea following indiscretions in diet, had suggested to her physician the possibility of pellagra, but no evidence was found in support of this diagnosis.

**Examination**—On examination, she was seen to be a thin, pale woman with well-marked pyorrhea alveolaris and gingivitis. The blood showed a profound secondary anemia. Repeated examinations of the stools revealed no ova or parasites, even after the administration of vermifuges. The gastric analysis was normal. A faint trace of albumin noted in the urine on the first examination soon disappeared. No casts were observed.

**Treatment and Course**—At the suggestion of the dental department,  $\frac{1}{2}$  grain of emetin hydrochlorid was administered subcutaneously each day for four days, beginning April 2. April 3 the patient had a slight chill, followed by an elevation of temperature to 101. April 4 a distressing diarrhea began, there were ten bowel movements during the night. She complained of aching all over, of pain in the back and abdomen, and of tenesmus. The stools at this time contained large numbers of leukocytes and a few red blood cells. No amebas were found. The leukocytes rose to 13,800. During the following six days there were from five to ten stools in the twenty-four hours, all containing pus and blood. April 9, albumin reappeared in the urine. April 11, six days after discontinuing the emetin, the diarrhea promptly stopped, and did not recur during her stay in the hospital. The albuminuria also disappeared.

Stool cultures, pelvic and protoscopic examinations were negative. Following the onset of the diarrhea, a toxic delirious state developed, with great mental confusion and visual and auditory hallucinations, necessitating the transfer of the patient to the Phipps Psychiatric Clinic. In the course of a week the psychosis cleared up, and she was discharged mentally and physically much improved.

A letter from her husband received July 15 states that "she is in better shape than she has been for twelve years, she weighs 110½ pounds—more than she has ever weighed in her life."

A second letter was received, October 1, saying that save for an occasional attack of migraine, and a feeling of weakness on exertion, the patient was doing well.

**SUMMARY**—An anemic, undernourished woman, weighing 95 pounds (43.2 kg), received subcutaneously  $\frac{1}{2}$  grain of emetin hydrochlorid daily for four days. An intense diarrhea developed, associated with abdominal pain and tenesmus, which ceased six days after discontinuing the emetin treatment. At the same time she was in a toxic delirious state, which lasted for one week. She recovered rapidly and left the hospital much improved.

The daily dose of emetin was  $\frac{1}{2}$  grain (30 mg) or 0.7 mg per kg. Two grains (120 mg) were given in toto, or 2.77 mg per kg.

The symptoms here following emetin administration were quite out of proportion to the moderate dosage employed, and the particular preparation was suspected of being unusually toxic. Accordingly, a dog weighing 10.5 kg was given 10 mg subcutaneously daily for three days. On the third day a bloody diarrhea set in and the animal died on the same day. At necropsy, an extensive hemorrhagic gastroenteritis was found. This dog received daily 1.0 mg per kg, or, in toto, 3 mg per kg—approximately the same relative dosage as had been given to the patient. It will be seen from the experimental observations which follow that this particular preparation of emetin was decidedly more toxic than usual.

#### EXPERIMENTS ON ANIMALS

Studies were made on sixty-two animals, the series comprising dogs, cats and rabbits. Five commercial preparations of emetin hydrochlorid were investigated: Burroughs Wellcome & Co., (ampoules); Eli Lilly & Co., (ampoules); Merck & Co., (crystals); Parke, Davis & Co., (ampoules); and Sharp & Dohme, (hypodermic tablets).

Injections were made in part subcutaneously, in part intravenously. The points particularly observed were (1) toxicity, (2) effects on the circulation and respiration, (3) pathological changes, (4) effect on the coagulation of the blood, (5) effect on renal function and the development of acidosis.

1 *Toxicity A. Subcutaneous Injections*—(See Table 1) Dogs receiving single small injections of 10 mg (1 to 2 mg per kg) show no appreciable reaction. Repeated daily injections of 10 mg cause death (usually with gastro-enteritis) in from three to fifteen days (average, seven to ten days). Either there is an actual cumulative action of the drug or an altered tissue response on the part of the animals.

Larger single subcutaneous injections of 30 to 45 mg (3 to 5 mg per kg) cause death in from two to five days. The same gastrointestinal lesions are found at necropsy.

Cats tolerate larger doses. Daily injections of from 2 to 5 mg per kg kill the animals in from seven to eleven days. As a rule, the anatomical lesions present are exceedingly slight. The results in kittens are essentially similar to those in adult cats.

In rabbits, daily doses of 5 mg (3 to 4 mg per kg) are uniformly fatal in from five to six days. As in cats, necropsy usually reveals but slight anatomical changes.



TABLE 1—SUBCUTANEOUS INJECTIONS

Species and Number of Animals Used	Preparation Used	Daily Dosage, Mg	Daily Dosage, Mg per Kg	Total Dosage, Mg	Total Dosage, Mg per Kg	Time Necessary to Kill, Days	Remarks
I Dogs 11	(A)	10	0.95 - 2.04 AV 1.54	30 - 90 AV 63.2	2.85 - 11.7 AV 8.83	3 - 11 AV 6.5	More than 50 per cent of the animals vomited one or two days prior to death. Diarrhea accompanied the vomiting in about a quarter of the animals. The lowest figures in this series are those resulting from the use of the unusually toxic preparation mentioned in the second case report.
	(B)	10	1.3 - 2.12 AV 1.71	60 - 100 AV 80	11.16 - 19.08 AV 13.58	8 - 13 AV 10.5	One animal alive but emaciated after nine days. Diarrhea and vomiting, in only one instance. Some pathological lesions, as with preparation (A). One animal (precipitant) had miscarriage on the tenth day, with birth of ten dead pups.
	(C)	10	1.02 - 1.6 AV 1.37	50 - 96 AV 72	8 - 10.43 AV 9.11	5 - 15 AV 9.5	Vomiting and diarrhea one or two days prior to death in two of the animals. Usual lesions.
	(A)	15 - 45	3.26 - 6.38 AV 4.44	30 - 90 AV 61.2	7.5 - 9 AV 7.62	2 - 6 AV 3	More acute poisoning. Same lesions. Vomiting and diarrhea usually on second day. Three of the animals died on second day. One, receiving the smallest doses, with two days' interval between injections, died on the sixth day.
	(A)	10	3.14 - 5.12 AV 3.97	60 - 100 AV 77.5	21.98 - 26.3 AV 30.25	7 - 10 AV 9.5	Vomiting and diarrhea on the second or third day preceding death in three animals. All drooled from the mouth when toxic symptoms became manifest.
II Cats 4	(A)	25 - 5	2.17 - 5.55 AV 3.0	12.5 - 27.5 AV 20	13.88 - 23.9 AV 19.89	1 - 7 AV 5.5	These animals were kittens. Lively until day of death.
	(B)	10	3.11	70	21.98	10	No vomiting or diarrhea.
	(C)	10	2.0 - 5.26 AV 3.22	60 - 100 AV 85	16.0 - 29.4 AV 23.5	9 - 15 AV 11	Vomiting in two of the animals.
	(D)	10	2.8 - 4.16 AV 3.48	70 - 100 AV 85	23 - 29.12 AV 23.56	7 - 11 AV 9	Diarrhea in one animal, vomiting in the other.
	(E)	10	4.0 - 4.76 AV 4.5	30 - 60 AV 47.5	14 - 27.24 AV 21.07	3 - 7 AV 5.5	No diarrhea or vomiting. Marked drooling from the mouth for two or three days prior to death.
III Rabbits 2	(A)	5	3.22 - 3.33 AV 3.27	20 - 25 AV 22.5	13.32 - 16.1 AV 14.71	5 - 6 AV 5.5	Muscular tremors in one animal just before death, in tetanic spasm for a short while.
	(C)	5	3.33 - 4.16 AV 3.75	20 - 25 AV 22.5	13.32 - 20.8 AV 17.6	5	

Differences in the time necessary to kill are dependent in part on variations in toxicity of the preparations used, and in part, perhaps, on varying degrees of resistance to intoxication of individual animals. Whatever the cause, these variations are extreme. In dogs, for instance, a total dosage of 3 mg per kg of the most toxic preparation given subcutaneously killed within three days, whereas, 19 mg, per kg of another commercial preparation required eleven days. In cats, 14 mg per kg (total dosage) of one preparation caused death in three days, whereas, 29 mg per kg of another killed only after seven days. For immediate death following intravenous administration, 4 mg per kg in one instance, and 18 mg per kg in another, were necessary.

The symptoms of intoxication as a rule manifest themselves two or three days before death. There is extreme muscular weakness and pronounced lethargy. The animals lie on their sides in the cages and are roused with difficulty. More than half of the dogs and cats vomit, many have numerous thin, unformed stools. Some of the dogs suffer from a bloody diarrhea, a few have large hemorrhages from the bowel on the day of death. Muscular tremors occur occasionally in dogs and rabbits. Drooling from the mouth is common, especially in cats.

B *Intravenous Injections*—(See Table 2) The lethal single intravenous dose is variable (4 to 18 mg per kg in dogs, 6 to 16 mg per kg in cats) and is largely dependent on amount, dilution and rapidity of injection. In exceptional instances, dogs may temporarily survive single injections of from 3.5 to 12 mg per kg, but death generally occurs within two days.

Vedder<sup>3</sup> has found that "2.5 mg per kg intravenously is the minimum fatal dose for rabbits, while one rabbit died as the result of 20 mg per kg administered subcutaneously. The rabbits to which the drug was given intravenously died in a few seconds, apparently as the result of centric paralysis. 10 mg per kg subcutaneously on two successive days is a uniformly fatal dose for white rats."

2 *Effects on the Circulation and Respiration*—Kymographic records were made with the animals under ether anesthesia and electrocardiograms were taken on chlorotoned dogs.

The subcutaneous injection of a relatively large dose (40 mg) in a dog weighing 10.2 kg caused no appreciable fall in blood pressure within fifteen minutes, at the end of half an hour the pressure had dropped from 150 mm to 100 mm Hg (See Fig 1). This was probably due in part to the influence of the anesthetic. There was no change in the animal's general condition. Single smaller subcutaneous doses of 10 mg (1 to 2 mg per kg) have no perceptible effects.

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3 Vedder, E. B. Jour Am Med Assn, 1914, lxii, 501

TABLE 2—INTRAVENOUS INJECTIONS

Species and Number of Animals Used	Preparation Used	Total Dosage, Mg	Amount of Dilution, cc	Total Dosage, Mg per Kg	Time Necessary to Kill, Days	Remarks
I Dogs 7	(A)	45 192 AV 106.5	4 - 200 AV 38	3.71 - 18.82 AV 9.68	Immediate death	Ventricular fibrillation with temporary spontaneous recovery. Bloody diarrhea on day of death. No vomiting. At necropsy, extensive hemorrhagic gastro enteritis with ulcers in the duodenum and upper jejunum.
	(C)	80	5	9 - 9.3 AV 9.15	Immediate death	
	(D)	60 120 AV 90	10 40 AV 25	5.71 - 11.12 AV 8.6	Immediate death	
	(A)	60	12	4.18	1	
	(C)	110 120 AV 115	10 - 21 AV 15.5	6.96 - 11.93 AV 9.15	2 3 AV 3.5	
1	(D)	60	10	4.91	2	One of the animals received two injections of 60 mg each, given at an interval of two days. Vomited on the third day and died with a bloody diarrhea on the fifth day. The other temporarily recovered from ventricular fibrillation, but died on the second day. At necropsy, gastro enteritis.
II Cats 3	(D)					No diarrhea or vomiting
	(A)	20 - 40 AV 27.3	3 - 25 AV 11	6.02 - 10.66 AV 9.91	Immediate death	

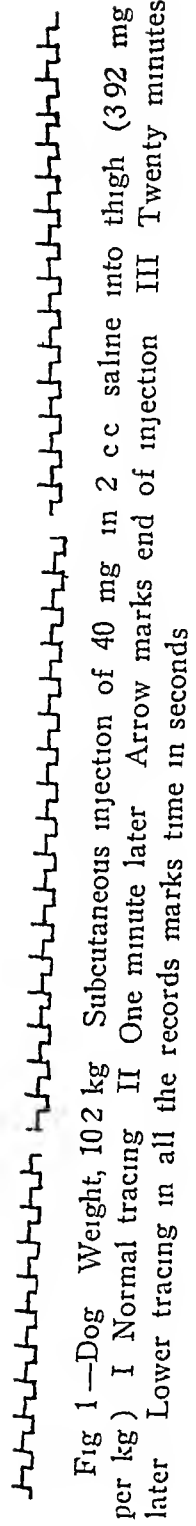
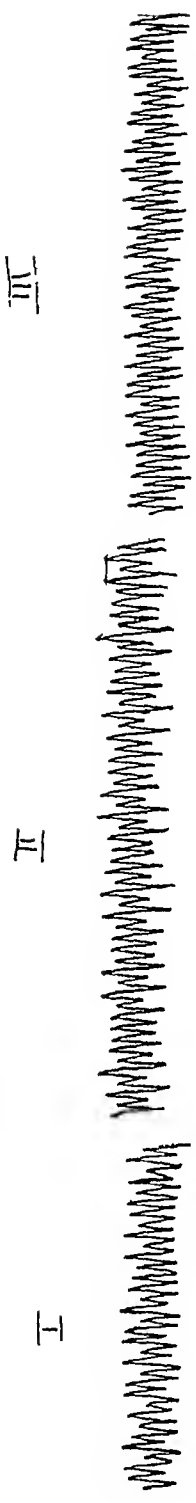


Fig 1—Dog Weight, 10.2 kg Subcutaneous injection of 40 mg in 2 cc saline into thigh (3.92 mg per kg) I Normal tracing II One minute later Arrow marks end of injection III Twenty minutes later Lower tracing in all the records marks time in seconds

In slowly poisoned animals, subjects of repeated small daily subcutaneous injections (1 to 2 mg per kg), there is a marked fall in pressure<sup>4</sup> coincident with the appearance of toxic symptoms. In one animal of 5.5 kg which received seven daily injections of 10 mg each, there was a difference of 100 mm between the original measurement and that taken on the day of death. The pulse in the sick animals is rapid and small.

The effect of intravenous injections depends on several factors (1) the quantity injected, (2) its dilution, (3) the rate of injection and to a lesser extent (4) the preparation employed, and (5) the individual susceptibility of the animal.

The first of these is obvious. Relatively small amounts (3 to 4 mg per kg) given in small volume (5 to 10 c c) and rapidly injected, cause an abrupt fall in blood pressure and death in a few minutes, heart and respirations stopping synchronously (Figs 2 and 3). The lethal effect is due mainly to the toxic action of the drug on the heart muscle proper, causing an acute cardiac dilatation. Whether there is at the same time a vasomotor paralysis is not clear. The venous congestion of the abdominal organs suggests that this element may play a rôle.

On the other hand, when the emetin is well diluted and slowly administered, tremendous doses may be well borne. One dog weighing 10 kg received 192 mg in 200 c c of salt solution during a thirty-minute period. Death followed a final rapid concentrated injection (40 mg in 10 c c). This animal received in all 18.82 mg per kg—an unusually large amount.

The various commercial preparations, as well as different lots from the same firm, vary somewhat in toxicity (Tables 1 and 2, and Case 2). Baermann and Heinemann<sup>5</sup> have made a similar observation. It is difficult to gauge accurately the extent of this variation, since animals, like human beings, apparently show differences in their individual tolerance for the drug.<sup>6</sup>

Following the intravenous injection of a non-lethal dose there is a prompt fall of blood pressure of from 20 to 140 mm Hg, varying according to the conditions of the injection. The pressure rapidly returns to its former or even to a higher level. There may be recovery from alarmingly low pressures (Fig 4).

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4 The apparatus devised by Dr B. B. Turner was used in making these determinations. (See Turner, B. B., Marshall, E. K., Jr., and Lamson, P. D. *Jour. Pharmacol. and Exper. Therap.*, 1915, vii, 129.)

5 Baermann, G., and Heinemann, H. *München med. Wchnschr.*, 1913, lx, 1132 and 1210.

6 This is exemplified by variations in tolerance to crystalline emetin. (See Table 1, Cats, Preparation E.)

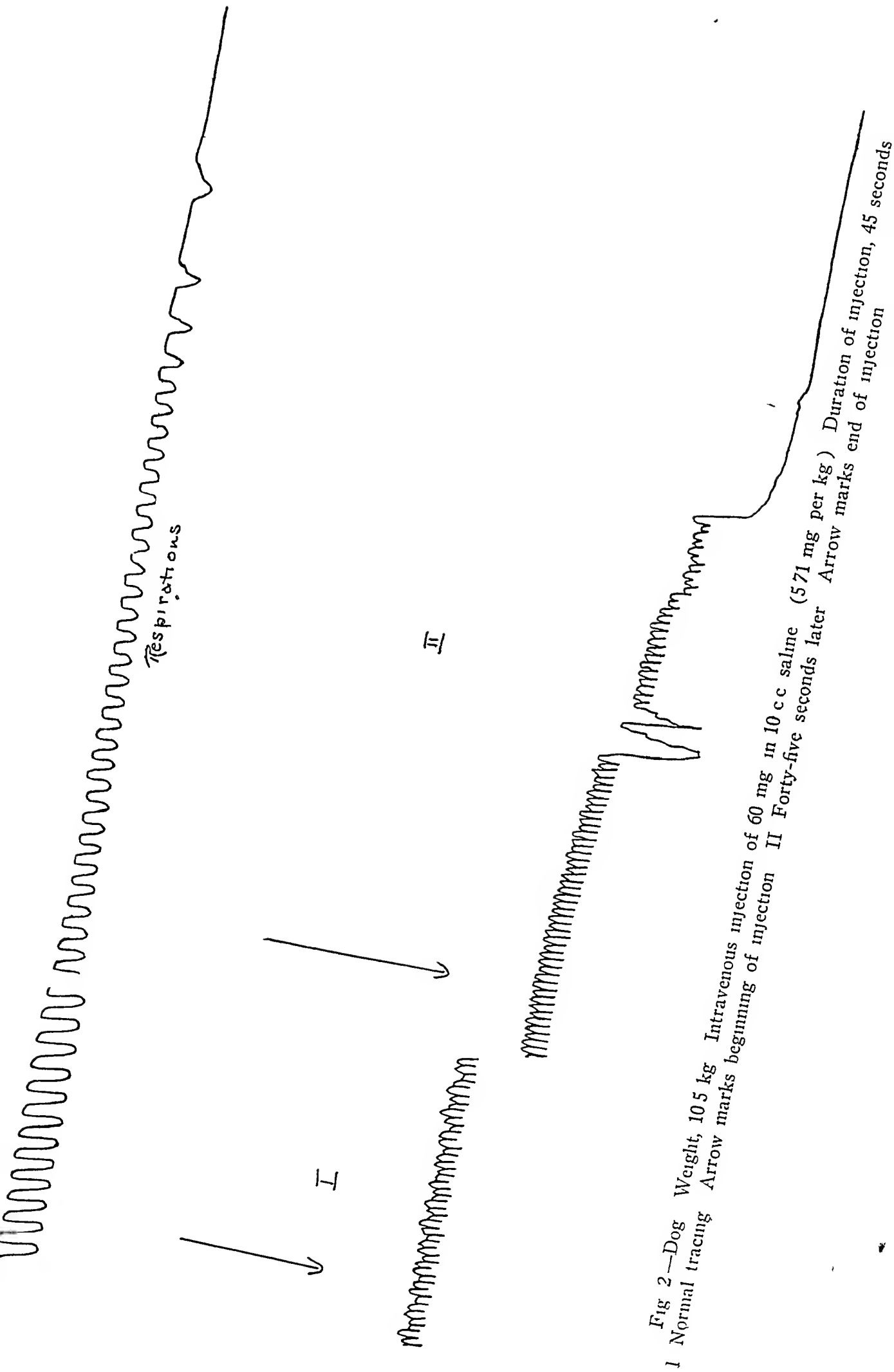


Fig 2—Dog

Weight, 10.5 kg

Normal tracing

Arrow marks beginning of injection

II

Forty-five seconds later

Arrow marks end of injection

Duration of injection, 45 seconds

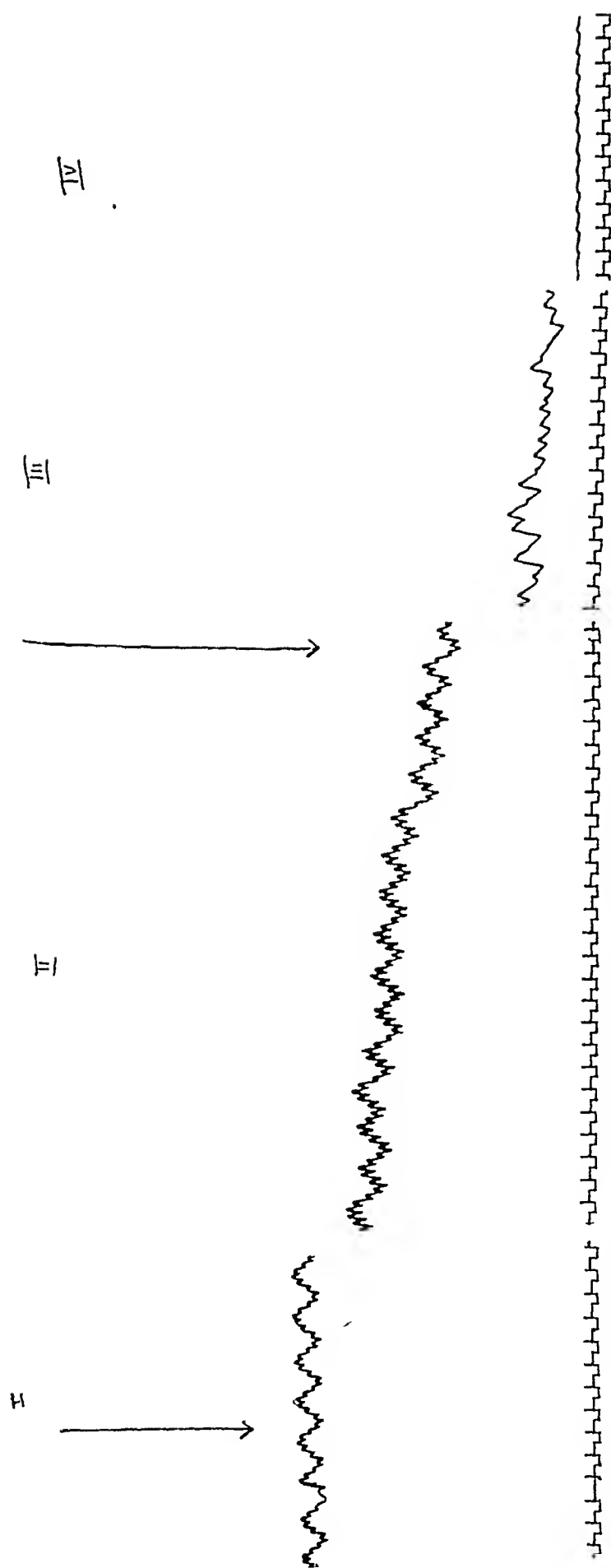


Fig 3—Cat Weight, 28 kg Intravenous injection of 20 mg in 20 cc saline (7.14 mg per kg) Duration of injection, 1 minute, 30 seconds I Normal tracing Arrow marks beginning of injection II One minute later Arrow marks end of injection III One minute later IV One minute later

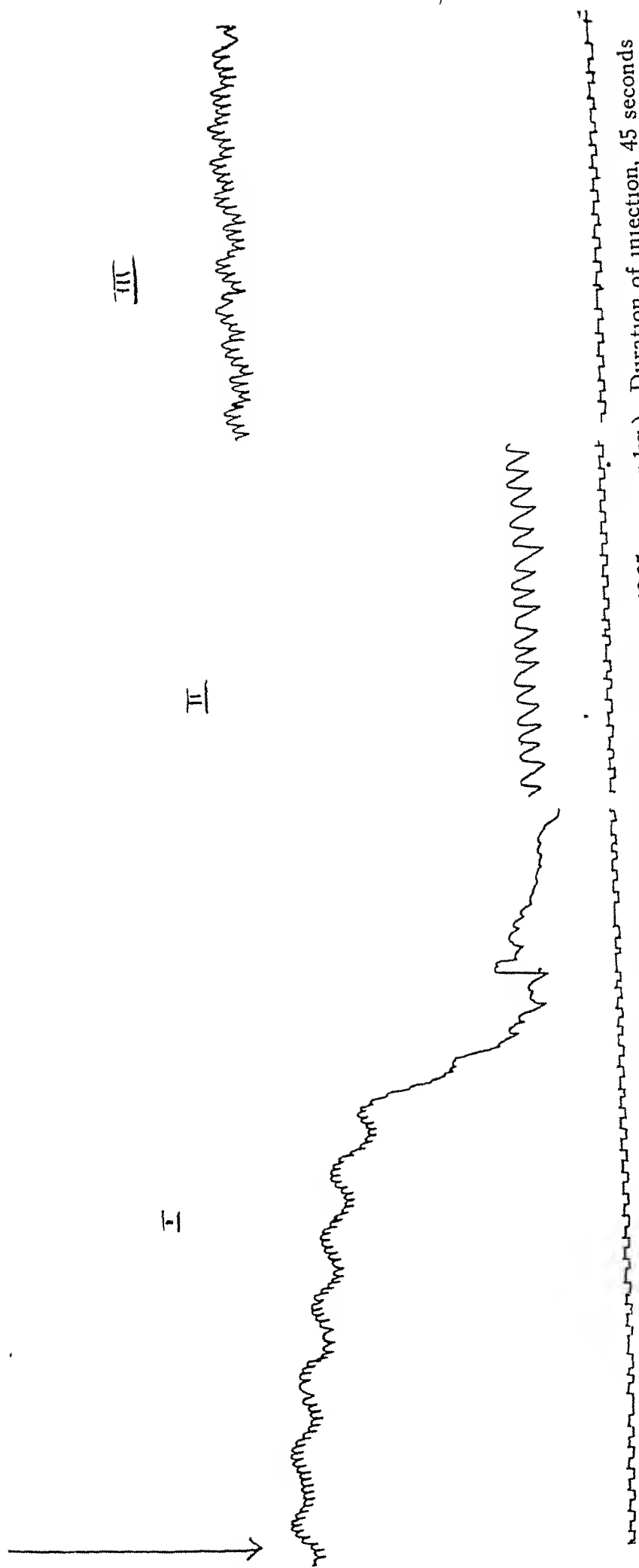


Fig 4—Dog Weight, 8.5 kg Intravenous injection of 20 mg in 10 c c saline (2.35 mg per kg) Duration of injection, 45 seconds  
 I Arrow marks end of injection II One minute later III Two minutes later



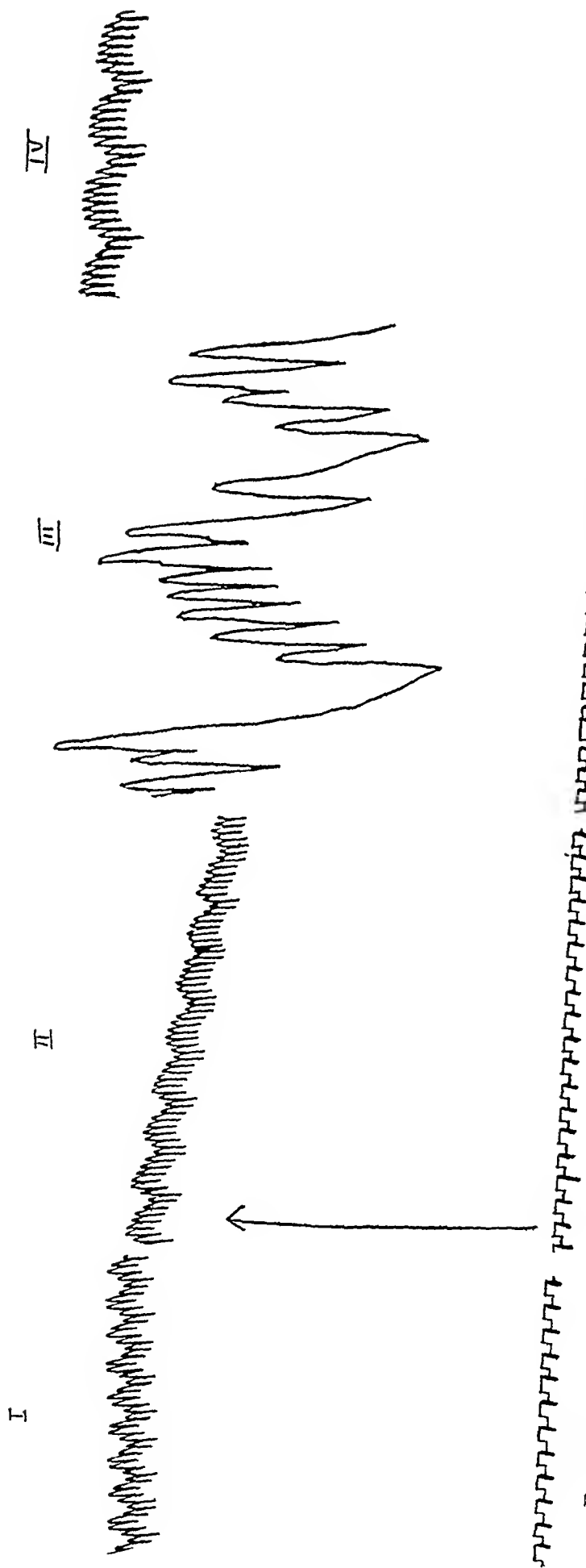


Fig 5—Dog Weight, 14.35 kg. Intravenous injection of 60 mg in 12 cc saline (4.18 mg per kg) I Normal tracing II Arrow marks end of injection, which lasted 2 minutes III Ventricular fibrillation, which continued for 5 minutes and 7 seconds IV Spon-

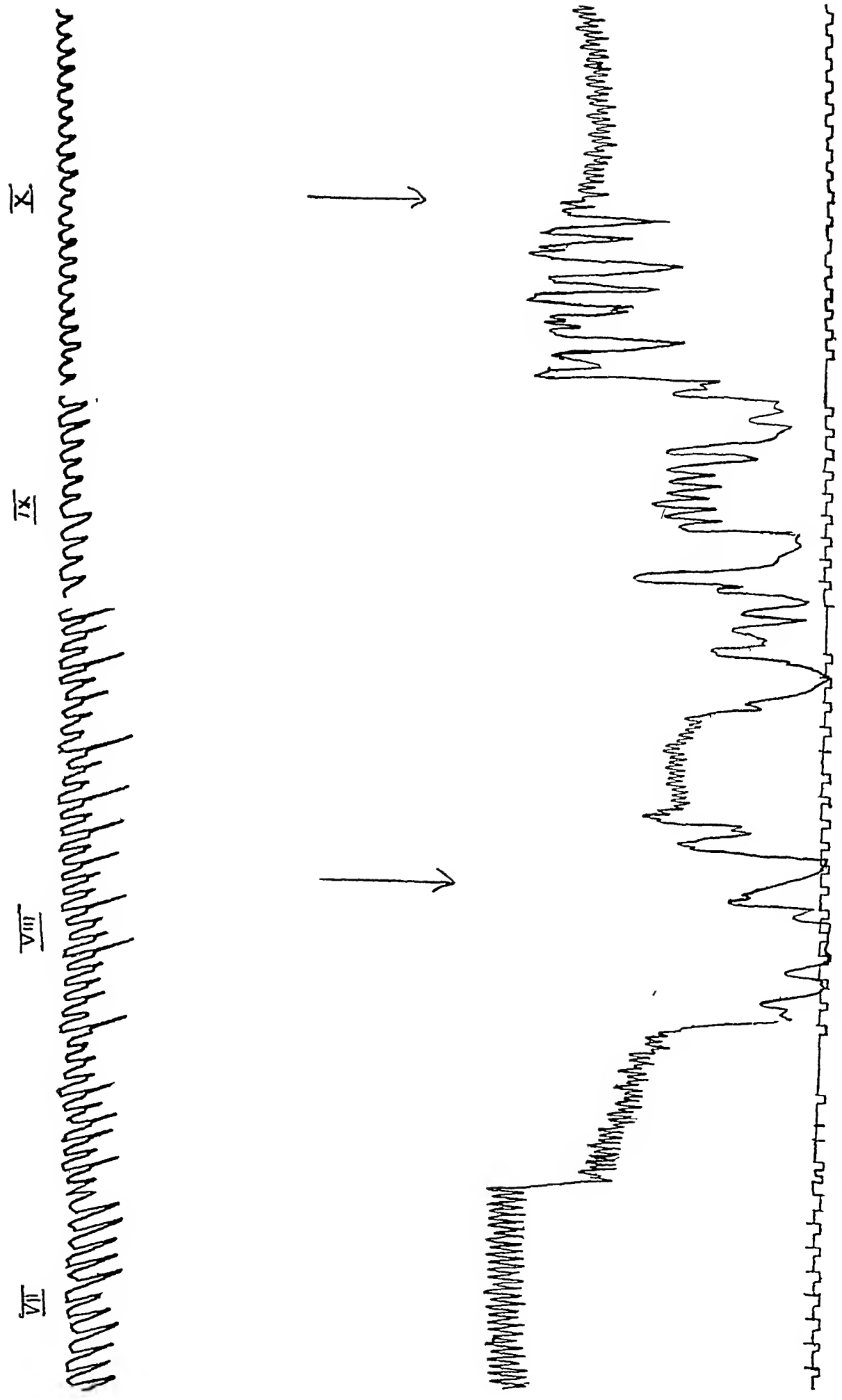


Fig 6—Dog Weight, 10.2 kg Intravenous injection ended at first arrow VII Normal tracing VIII and IX Ventricular fibrillation X Spontaneous resumption of normal rhythm at point indicated by second arrow Upper tracing records respirations

In some of the animals a remarkable cardiac arrhythmia is observed. There is a sudden transition from the normal kymographic tracing to one showing wide, irregular sweeps (Figs 5 and 6). An abrupt fall in blood pressure and death from acute cardiac dilatation may follow this irregularity, or the normal tracing, at a higher level, may be resumed (Figs 5 and 6). Electrocardiographic studies have shown that this irregularity is due to a coarse type of ventricular fibrillation<sup>7</sup> (Fig 7).

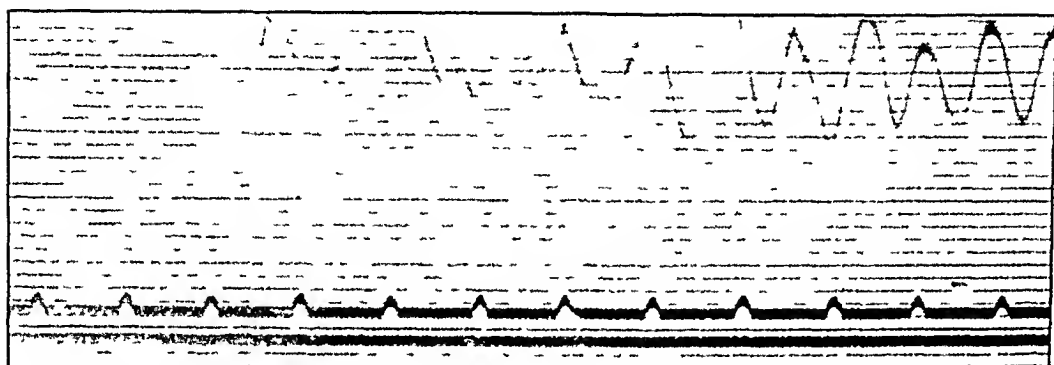


Fig 7—Dog. Weight, 86 kg. Received 275 gm chlorotone by stomach tube one hour prior to injection, 80 mg in 5 cc salt solution intravenously injected (93 mg per kg). Electrocardiogram (taken by Dr Bridgman) shows transition to coarse type of ventricular fibrillation.

In order that the mechanism of cardiac death might be observed, median thoracotomy was done in an animal receiving intratracheal anesthesia. There was at first generalized fibrillation of auricles and ventricles. The auricles then ceased to contract, becoming engorged.

<sup>7</sup> Ventricular fibrillation has been previously observed in experimental animals, but usually as a terminal event. Levy and Lewis have produced it in cats by administering low tensions of chloroform vapor together with small intravenous injections of adrenalin chlorid (Levy, A. G., and Lewis, T. Heart, 1911-12, iii, 99). Levy, continuing these experiments, states that "spontaneous recovery in the cat is not infrequent, it may occur after a few seconds of fibrillation, or indeed after a period of one or more minutes. As a general rule, however, the heart neither recovers spontaneously nor can it be restored to its normal function by any method in general use for the treatment of cardiac syncope, and it eventually dies from asphyxia of its tissues" (Levy, A. G. Heart, 1912-13, iv, 319).

In human beings, fibrillation of the ventricles has occurred either as a terminal phenomenon (Halsey, R. H. Heart, 1915, vi, 67) or immediately after clinical death (Robinson, G. C. Jour. Exper. Med., 1912, xvi, 291).

Lewis (Osler and McCrae's Modern Medicine, iv, 106) states "Fibrillation in the ventricles is similar to the condition of fibrillation in the auricles, when it comes, coordinate systole in the ventricle is suspended and the muscle exhibits a continuous quivering and ineffective movement. Its onset spells death. In animals under experimental conditions it is of extremely common occurrence, the circulation is immediately brought to a standstill, and the animal, after a few gasping respirations and twitching movements of asphyxial origin, remains perfectly quiescent."

Hoffman (Heart, 1911-12, iii, 213) has observed in a woman, recovery from fibrillation of the ventricles which lasted for two seconds at the end of an attack of paroxysmal tachycardia.

and dilated. The ventricles continued to fibrillate for a time, finally only the left ventricle near the apex of the heart continued in this fashion. Fibrillary contractions persisted for five or ten minutes after the heart had ceased beating. In several instances, especially in cats, the heart of the animal, studied immediately after death, continued to fibrillate for as long as fifteen minutes. In a few, the left ventricle was found firmly contracted in systole, the right flabby and dilated.

There is no significant change in respiration (Figs 2 and 6) until just before death. Then there are asphyxial gasps at long intervals. Artificial respiration is unavailing in restoring the heart when once it has ceased to beat. Usually heart and respiration stop practically synchronously (Figs 2 and 8).

Cutting the vagi before or after the injection produced no effect in the response (Fig 8).

*3 Pathological Changes*—In dogs, the characteristic lesion is an inflammation of the gastro-intestinal tract. The earliest change is observed in an animal acutely poisoned by intravenous injection and dying at the end of about an hour. There is well-defined injection and swelling of the mucous membrane of the small intestine, especially of the ileum. When death occurs within a few minutes the heart is found tremendously dilated, in diastolic standstill. Where smaller quantities are injected intravenously, or daily subcutaneous injections are given over a longer period, and the animal survives for twenty-four hours or more, there is a severe gastro-enteritis, often hemorrhagic in character. The mucous membrane of the intestine is swollen, its vessels are engorged and a mucopurulent exudate may cover portions of its surface. Submucous ecchymoses are not uncommon. The ileum appears to suffer most, although the entire gastro-intestinal tract, "from cardia to anus," is sometimes filled with a bloody, mucoid material. In two animals several sharply-defined, punched-out ulcers were present in the duodenum and upper jejunum.

Microscopically,<sup>8</sup> there is marked congestion and edema of the mucosa, submucosa and muscularis present similar but less marked changes. The adjacent mesenteric fat may be congested and swollen.

All the abdominal organs are engorged with blood. The liver and kidneys, both grossly and microscopically, show congestion and cloudy swelling. A few small hemorrhages are sometimes observed in the renal medulla. In one instance the entire head of the pancreas was surrounded and infiltrated by extravasated blood, which under the microscope was seen to have forced its way between the lobules. In this same animal there was a subcapsular hemorrhage into the cortex of the kidney. Bronchopneumonia and pulmonary edema each were observed twice in association with the usual intestinal lesions.

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<sup>8</sup> We are indebted to Dr T P Sprunt for notes on the microscopic pathology.

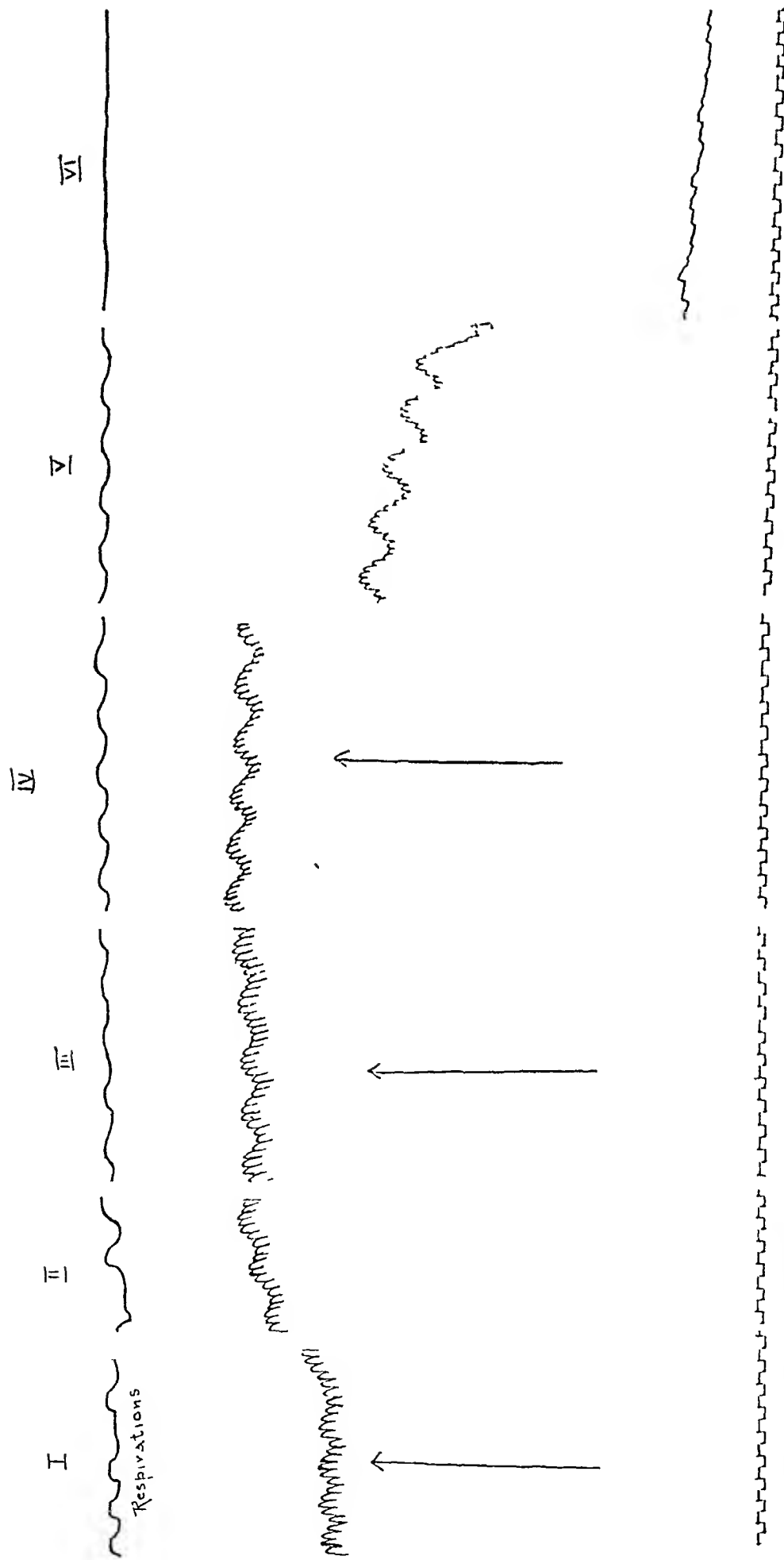


Fig 8—Cat Weight, 3.65 kg Cutting of vagi, followed by intravenous injection of 22 mg in 3 cc saline (602 mg per kg)  
 I Arrow indicates cutting of left vagus II Thirty seconds later III One minute later Arrow indicates cutting of right vagus  
 IV Two minutes later Injection begun at arrow, duration, 45 seconds V One minute later VI One and one-half minutes later

In *cats and rabbits*, pathological changes are slight and inconstant. There is generally some injection of the vessels of the upper portion of the small bowel. The liver and kidneys are congested, and in slowly poisoned animals show cloudy swelling. In one cat, hemorrhage occurred in the cecal region, in another there was a mild grade of pulmonary edema.

The tendency for rabbits poisoned by emetin occasionally to develop hemorrhagic pulmonary lesions has been noted by a number of previous observers. This has been confirmed by finding in one of our animals a patchy, hemorrhagic bronchopneumonia with actual bleeding into the lung tissue. Microscopically, there could be seen several points of rupture in the smaller arteries of the lung, from which blood was pouring into the alveoli.

4 *Effect on the Coagulation of the Blood*—It was noted that the blood of poisoned animals clotted unusually slowly and that the clot was nonretractile in character. Several specimens of blood were examined by Professor Howell, who has very kindly made the following notes:

Dog 1—Weight, 10 kg. Given 45 mg. emetin hydrochlorid subcutaneously. On the following day, profuse, bloody diarrhea and vomiting. Death on third day. Blood for examination taken on second day, collected in oxalate solution, plasma yellowish.

The oxalated plasma with thrombin solutions gave a clear, solid clot which was entirely nonretractile, having the same soft, jelly-like consistency that is obtained in blood to which  $\text{Na}_2\text{CO}_3$  has been added to distinct alkaline reaction. This plasma, tested with neutral red, gave a reaction toward the acid side. Under the ultramicroscope,<sup>9</sup> the clot showed no visible structure whatever, whereas, the normal clot shows a mass of interlacing needles or spicules.

Dog 24—Weight, 14.5 kg. Received 60 mg. emetin hydrochlorid intravenously. Died in thirty hours with a hemorrhagic gastro-enteritis.

A specimen of blood was taken immediately after death, oxalated and centrifugalized. Plasma very scanty in amount (about half normal) and yellowish in color. When thrombin solutions were added, clotting was slow and imperfect, as though fibrinogen were deficient in amount. The final result was a floating clot.

Under the ultramicroscope some fibrin needles formed but were scanty—scattered needles or small clumps of needles in place of the thickly meshed needles of normal plasma.

5 *Studies of Renal Function and Acidosis*—Several dogs were used for this purpose. Albuminuria occurred inconstantly in slowly poisoned animals. There was no appreciable reduction in 'phthalein excretion, nor was there any nitrogen retention as evidenced by the urea content of the blood, even on the day preceding death. As a terminal phenomenon, on the day of death there was noted very slight increase

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<sup>9</sup> In this connection see article by Prof. Howell, *Amer. Jour. Physiol.*, 1914, xxxv, 143.

in the hydrogen-ion concentration of the blood serum, but no change in that of the whole blood<sup>10</sup> The  $\text{CO}_2$  tension of the alveolar air was also somewhat lowered, in one animal falling to 33 mm Hg several hours before death This phenomenon has been noted by Meyer and Williams<sup>11</sup> in experimental emetin poisoning

#### SUMMARY OF PREVIOUS EXPERIMENTAL WORK ON EMETIN

In 1817, Magendie and Pelletier<sup>12</sup> announced that they had isolated an emetic substance ("*matiere vomitive*") from the plant *psychotria emetica* This substance they called emetin They found that it had an emetic and purgative action and that it possessed marked narcotic properties when given to animals In order to determine the toxicity of the drug, 10 grains were given to a dog Vomiting and stupor followed, and the animal died in fifteen hours "Anatomical examination showed that the animal had succumbed to a violent inflammation of the tissue of the lungs and of the mucous membrane of the intestinal tract, from cardia to anus" After obtaining similar effects with a number of animals, they concluded that "these observations are important, inasmuch as they show that emetin, given in large doses, may produce grave results"

During the remainder of the nineteenth century, a number of investigators undertook the study of ipecacuanha and its newly discovered alkaloid Especially notable for their completeness and accuracy of observation are the articles of Dyce Duckworth<sup>13</sup> and Podwyssotzki<sup>14</sup> The latter noted with wonder the cardiac arrhythmia which we have shown to be due to ventricular fibrillation

Of fundamental importance was the work of Paul and Cownley<sup>15</sup> in 1893 demonstrating that the so-called emetin of previous workers was in reality a mixture of two alkaloids—the one, emetin, an amorphous substance, to which they assigned the formula  $\text{C}_{11}\text{H}_{17}\text{NO}_2$ , the other, which they named cephaelin, a crystalline substance having the formula  $\text{C}_{11}\text{H}_{19}\text{NO}_2$  Emetin hydrochlorid,  $\text{C}_{11}\text{H}_{17}\text{NO}_2\text{HCl}$ , they were able to make in crystalline form The presence of a third alkaloid, psychotrin, was determined by them two years later<sup>16</sup> It was isolated in small amounts as lemon-yellow, rhombic prisms The amount of alkaloids in ipecacuanha they found to be about 2 per cent

Wild<sup>17</sup> in 1895, working for the first time with these pure alkaloids, which he obtained from Paul, investigated and compared their pharmacological action He found that both emetin and cephaelin are emetics, the emetic dose of the latter being half that of emetin Both lower the blood pressure The depression produced by the emetic dose of cephaelin is less than that produced by the larger emetic dose of emetin The vascular effects from emetin are greater Both produce weakening, slowing and diastolic arrest of the heart

10 In making these determinations, the method recently described by Levy, Rowntree and Marriott was employed (THE ARCHIVES INT MED, 1915, xvi, 389)

11 Meyer and Williams Arch f exper Path u Pharmacol, 1881, xiii, 70

12 Magendie and Pelletier Jour de pharin, 1817, iii, 145

13 Duckworth, Dyce St Bartholomew's Hosp Rep, 1869, v, 218, also 1871, vii, 91

14 Podwyssotzki Arch f exper Path u Pharmacol, 1879, xi, 231

15 Paul, H B, and Cownley, A J Pharm Jour and Trans, 1893, liii, 61, also 1894, liv, iii

16 Paul, H B, and Cownley, A J Pharm Jour and Trans, 1895, liv, 690

17 Wild, R B Lancet, London, 1895, ixxiii, 1274

Lowin<sup>18</sup> in 1902, in a review of previous work on the subject, gives a complete bibliography to date. In addition to the facts emphasized by Wild, he confirms the characteristic gastro-intestinal lesions found by others in poisoned animals, and states that on the lungs emetin has no action, whereas, in cephaelin poisoning, extravasation of blood into the lungs was noted several times. Deleterious action on the kidneys is found to be more characteristic of cephaelin. Poisoned animals die of cardiac paralysis. Emetin, however, injures the heart in much smaller doses than does cephaelin, but cephaelin causes a greater fall in blood pressure.

The mode of excretion of the alkaloids could not be determined by Lowin. No trace of them was found in gastric or intestinal contents or in the urine.<sup>19</sup> Finally, he determined that psychotrin need not be considered in taking into account the action of these alkaloids, it is present in very small amounts, has no emetic action and no toxic action on the heart.

Our pharmacological and pathological findings are quite in accord with those of previous investigators, while two new facts are contributed. First, by electrocardiographic studies it has been shown that the cardiac irregularity produced in emetin poisoning is due to fibrillation of the ventricles, from which the animals may recover, and, second, Professor Howell's observations have shown alterations in the clotting properties of the blood.

#### ILL EFFECTS FOLLOWING THE CLINICAL USE OF EMETIN

That the therapeutic administration of emetin should not be regarded as an altogether innocuous procedure has been previously noted. Thus, even as early as 1895, Wild<sup>17</sup> says "The fact that a dilution of 1 in 20,000 caused diastolic arrest of the frog's heart in forty-six minutes, renders caution necessary in giving larger doses of the alkaloid."

Baermann and Heinemann<sup>5</sup> have noted distressing and even alarming symptoms following doses much larger than are usually employed. They say "Subcutaneous injections produce in some instances slight general malaise, otherwise, with small and moderate sized doses of 60 to 150 mg, there are no symptoms. If 120 to 150 mg are given in daily repeated injections, there appear, after three or four injections, malaise, lassitude, slight vertigo and loss of appetite. These symptoms disappear in from 24 to 72 hours after the emetin has been discontinued.

"Intravenous injections of 60 to 200 mg cause no serious disturbance, there is slight vertigo, transient flushing of the face and retching. If this dosage is exceeded and 300 to 400 mg are injected, serious symptoms are observed. These appear in from two to five minutes after the injection and consist of general vascular paralysis, severe expiratory dyspnea with cessation of respiration, loss of consciousness with vomiting, the passage of thin stools, and great slowing of the pulse. Although these phenomena are transient and are quickly

18 Lowin, C. *Arch. internat. de pharmacod. et de therap.*, 1902, 21, 9.

19 More recently, Lyons (*New Orleans Med. and Surg. Jour.*, 1912, 111, 884), using sterilized fecal filtrates made from the stools of individuals receiving ipecac by mouth, could demonstrate no amebicidal properties, in vitro, of the contents of the bowel.



TABLE 3—REPORTED CASES IN WHICH ILL EFFECTS FOLLOWED THE CLINICAL USE OF EMETIN

Case No	Observer	Dosage and Mode of Administration	Total Dosage	Symptoms	Remarks
1	Allen <sup>1</sup>	1 gr subcutaneously	1 gr	Nausea for several hours, vomiting once, four hours after injection	Prompt recovery
2	Chauffard <sup>2</sup>	100 mg in 1 liter of water as rectal irrigation, patient had previously received subcutaneous emetin medication	100 mg (1½ gr)	Tremendous diarrhea same day—1½ dysenteric stools, containing mucus and blood	Patient was having only two or three stools daily when irrigation was given no further symptoms
3	Spehl and Colard <sup>3</sup>	30 mg twice a day for six days, followed by 30 mg three times a day for 13 (?) days	1.17 gm (19.5 gr)	Lassitude followed four days later by flaccid paralysis of all muscles, difficulty in chewing, swallowing and articulating heart rapid and beating feebly volume of urine normal, no albuminuria, but diminution in amount of urea and chlorides excreted, temperature normal, cutaneous and deep reflexes present but diminished, face edematous	Condition very alarming paralysis of muscles of respiration was feared Improvement began ten days after onset of symptoms, practically complete recovery in two weeks
4	Lshleman <sup>4</sup>	1 gr subcutaneously twice a day for five or six days	5-6 gr	Purpuric eruption consisting of dark red, discrete patches, terrific peripheral neuritis, involving chiefly legs, arms only slightly affected, edema of legs, patellar reflexes absent	Eruption persisted for six weeks, neuritis gradually subsided
5 and 6	Wels <sup>5</sup> (2 cases)	Not stated		Peripheral neuritis	
7	Lyons <sup>6</sup>	½ gr subcutaneously and ¼ gr by mouth twice a day for two days (i.e., 1½ gr daily)	2½ gr	Abdominal discomfort, diarrhea	Symptoms disappeared on stopping the drug by mouth
8	Lyons <sup>6</sup>	1 gr subcutaneously daily for two weeks, then 1 gr by mouth daily for ten days	2½ gr	Diarrhea, emaciation, weakness, blood, pus and mucus in stools but no amebae	Slow recovery
9	Lyons <sup>6</sup>	½ gr subcutaneously daily for three days, then 2 gr daily for four days	9 gr	On fourth day, diarrhea and abdominal discomfort, no amebae in stools	Bowel disturbance disappeared in two or three weeks

10	Lyons <sup>6</sup>	1 gr subcutaneously for twelve days	12 gr	Diarrhea, stools contained bloody mucus and a few resting amebae	Emetin stopped, saline enemas for five days, followed by another short course of emetin by needle, after which stools became normal. Neuritis gradually cleared up
11	Lyons <sup>6</sup>	1½ gr subcutaneously daily for six teen days	21½ gr	Mild peripheral neuritis in legs, some general muscular weakness	When seen six months later, was just recovering use of hands and feet
12	Hume <sup>7</sup>	¾ gr twice a day for seven days, then intravenously for a few days, then ½ gr daily subcutaneously for seven days	12½ gr	Peripheral neuritis, with double wrist and foot drop	
13 to 18	Hume <sup>7</sup> (6 cases)	Not known		Peripheral neuritis, resembling beriberi	
19	Levy and Rowntree	¼ gr subcutaneously three times a day for nine days, then ½ gr three times a day for two days, followed by ½ gr three times a day for nine days	29 gr	Diarrhea, muscular weakness, evidence of acute renal insufficiency with nitrogen retention and low phthaloin output, death	These cases occurred in a series of 100 cases of amebic dysentery treated with emetin. All cleared up on discontinuing the emetin
20	Levy and Rowntree	¼ gr subcutaneously daily for four days	2 gr	Diarrhea with blood and pus in the stools, development of toxic delirious state	Necropsy showed chronic passive congestion of viscera, a few echinocysts in the pelvis, a few tortions of the cortical striations, and bronchopneumonia

I Allen Jour Am Med Assn, 1913, lx, 664  
 Chauffard Presse med, 1913, xvi, 521

In the wards of the Johns Hopkins Hospital, high enemas of emetin (15 mg in 250 cc of water) have not proved disas-  
 trous (Case 2) In several instances, effectual bowel movements were obtained in constipated individuals It is possible that  
 purgative enemas of emetin may prove to be of some value as an aid in the treatment of constipation Rectal irrigations with  
 solution, more dilute than those employed by Chauffard deserve further trial in amebic infections

3 Spohl and Colaid Province med, 1914, xxvii, 176 (Abstract)  
 4 Eshleman Bull of Touro Infirmary, New Orleans Med and Surg Jour, 1914, lxi, 965  
 5 Weis Ibid (Note 4)  
 6 Lyons Am Jour Med Sc., 1915, cl, 97  
 7 Hume Personal communication Dr E H Hume of the Yale Medical College, China, has kindly permitted us to cite these cases They are to be reported shortly in the China Medical Journal

relieved by suitable measures, yet on the basis of these observations we would regard as the maximal intravenous dose 250 mg per kg of body weight. We have never observed any injury to the kidneys, nor has there been any permanent damage to the patient, even with the high intravenous doses."

Vedder's<sup>3</sup> comments in this connection are worth quoting in full. He says "Since emetin, by many observers, has been regarded as a more or less harmless drug, and since I am of the opinion that the doses used by some, and particularly by Baermann and Hememann, are too large, I wish to point out the possible danger in not using due caution in the use of this very potent remedy."

"It would appear from our experimental observations that the doses proposed by Baermann and Hememann are far too large, and that if the drug is administered in such doses, fatalities will soon occur which will unjustly discredit the use of emetin. Furthermore, these tremendous doses appear to be entirely uncalled for, since success is commonly obtained in the treatment of amebic dysentery and hepatic abscess with doses not exceeding 1 grain hypodermically."

"After seeing rabbits die immediately after intravenous injections of comparatively small amounts (from 3 to 5 mg) of emetin hydrochlorid, *I should hesitate before administering even 1 grain intravenously in a human case*"<sup>20</sup> If given to one of the patients so susceptible to the effects of ipecac mentioned by Sollmann<sup>21</sup> such a treatment would not improbably be followed by death."

Lyons<sup>22</sup> from clinical observations warns against the use of large doses, as follows "Too large doses or too prolonged use of moderate doses may cause a diarrhea or be responsible for its persistence. *There is increasing evidence that large doses of emetin are not without ill effect*"<sup>23</sup>

The reported cases in which ill effects have followed the clinical use of emetin are given in the accompanying table (Table 3)

The experience of Lyons<sup>22</sup> with the administration of emetin by mouth precludes its use by the oral route. He found it exceedingly irritant even in small doses. Nausea, vomiting, griping, purgation and persistent abdominal discomfort followed the ingestion of 1/2 gr in solution.

The case reported in detail earlier in this paper is the first in which the fatal result can be attributed to the therapeutic use of emetin. Only one fatal case of ipecacuanha poisoning could be found in the literature<sup>23</sup>

<sup>20</sup> Italics ours

<sup>21</sup> Sollmann, T. Text Book of Pharmacol., p. 309 (Cited by Vedder) "Some persons are so sensitive to the local action of ipecac that the opening of a jar at a distance of several feet will produce violent sneezing and discomfort."

<sup>22</sup> Lyons, R. Am Jour Med Sc., 1915, cl, 97

<sup>23</sup> Harrison (Lancet, London, 1908, ii, 536) tells of a 20-year-old youth who "drank several inches of a bottle of vinum ipecacuanhae." One hour after swallowing this dose there was uncontrollable vomiting and a rapid pulse, the extremities became cold and damp with perspiration. Death occurred in an hour and a half. At necropsy there was found subacute congestion of the stomach and first two feet of the intestine. The heart was in diastole. The other organs were normal. Harrison comments that "the congestion of the stomach was certainly an insufficient cause of death."

## SUGGESTIONS WITH REGARD TO A RATIONAL EMETIN THERAPY

How may the toxic effects of emetin best be avoided? As the result both of clinical and laboratory observations the following suggestions are presented

1 The administration of emetin hydrochlorid is not to be regarded as a harmless procedure. Even in therapeutic doses ill effects may follow its use.

2 Individualization by close clinical observation is essential both for the success and safety of the treatment. Patients may differ markedly in their susceptibility to the drug, and the various commercial preparations vary widely in toxicity. These points are strikingly demonstrated by the toxicity experiments herein reported.

3 The treatment should be given in courses, at intervals of several days or a week. The subcutaneous route is the one of choice. Individual dosage and the duration of each course must be determined by the exigencies of the case. One-third grain three times a day for a week or ten days is usually a safe dosage in amebic infections. It is rarely necessary to give more than  $1\frac{1}{2}$  grains daily. In the treatment of pyorrhea, Bass and Johns<sup>24</sup> advocate  $\frac{1}{2}$  grain daily for from three to six days, and maintain that no case need have more than six days' treatment. Under ordinary circumstances this seems well within the margin of safety. It must be borne in mind, however, that the administration of even relatively small doses over a long period of time may prove harmful.

4 The large dosage advocated by Baermann and Heinemann is unnecessary and dangerous.

5 Intravenous injections should be employed only in extreme cases. If this mode of administration seems imperative, small doses, well diluted ( $\frac{1}{2}$  grain in 100 c c salt solution) should be slowly given, and the blood pressure should be carefully observed during the injection.

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24 Bass, C C, and Johns, F M. Jour Am Med Assn, 1915, LXIV, 553

# THREE CASES OF PURPURA HEMORRHAGICA IN CHRONIC TUBERCULOSIS

WITH A BRIEF REVIEW<sup>4</sup>

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The subject of purpura in this paper is treated from the standpoint of the relationship it bears to tuberculosis

Several writers within the last two centuries have made observations on this phenomenon, endeavoring to find its cause and effect, and to discover the relation purpura has to other diseases with which it is associated

Mackenzie<sup>1</sup> says

The great variety of supposed causes or associated conditions is sufficiently striking. Still more so is the fact that in one-third of 200 cases no explanation was offered for the purpura, though in several of the cases a necropsy was made. It will thus be seen how extremely complex is the pathology of purpura.

All we can do in the present state of our knowledge is to accumulate further information and to exhaust every means—histological, bacteriological and chemical—in the investigation of cases.

Osler<sup>2</sup> also maintains "that purpura is obscure, and is an interesting manifestation of which we know so much and at the same time so little."

We may safely say, however, that the purpura observed in the three cases herein reported shows a striking relation between it and chronic tuberculosis. We may also claim that purpura is not of obscure origin, but that it has a definite mechanico-toxic cause.

The following are observations made by various authors who have given attention to this subject.

Osler claims that "purpura hemorrhagica rarely occurs with tuberculosis, but a fatal case has been reported."

Dieulafoy<sup>3</sup> divides purpura into different groups according to the diseases with which it is associated, as follows:

- 1 The nervous, as in tabes, myelitis and cancer of the spine
- 2 Medicinal, as in copaiba, belladonna, iodin and snake venom poisoning
- 3 The rheumatoid, as in peliosis rheumatica of Schoenlein
- 4 Infectious variola, erysipelas, typhoid, septicemia, infective endocarditis and pyemia
- 5 Necrotic purpura, as in gangrene
- 6 Acute pulmonary tuberculosis

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\* Submitted for publication Dec. 4, 1915

\* From the Tuberculosis Department of the Montefiore Home and Hospital

1 Allbutt's System of Medicine, vi

2 Osler's Modern Medicine, iv

3 Dieulafoy Principles of Medicine

Struempell<sup>4</sup> endeavors in his classification to show that purpura has its origin in an infection of some sort. Rosenow of Chicago holds the same view. Struempell claims that if rabbits are inoculated with the blood of a patient having purpura the animal will show similar cutaneous symptoms. This tends to show that whether it is in typhoid, septic endocarditis or rheumatic fever there is some bacillus or coccus that is the direct etiological factor.

Adam<sup>5</sup> attributes the causes of all purpura to a poison which acts on the endothelium of the smaller cutaneous vessels, producing fatty degeneration. It is the weakening and necrosis of these cells that would seem to precede the hemorrhage by rhexis or diapedesis which set up the purpura or ecchymosis.

Woodhead offers similar explanations of those of Adam.



Fig 1—Showing purpuric areas on arms of patient G I (Case 3)

Muir and Ritchie<sup>6</sup> claim that "in some cases of acute tuberculosis, when the bacilli become lodged in a capillary, the endothelial cells of its wall may proliferate, and thus a ring of nuclei may be seen round a small central thrombus."

Unna<sup>7</sup> acknowledges that from the information he received from others and from the results of his own wide experience, he fails to understand how a capillary hemorrhage is brought about. He claims that it is neither by the ordinary understood rhexis or diapedesis, that capillary hemorrhages are produced. There must be, he says, a specific cause or a "blind force" which renders these small cutaneous vessels

4 Struempell's Text Book on Medicine

5 Adam's Principles of Pathology

6 Muir and Ritchie Manual of Bacteriology

7 Unna Histopathology of the Diseases of the Skin

subject to hemorrhage His arguments against the accepted theories regarding these purpuric areas follows

- 1 The blood vessels of the skin are not disposed to hemorrhage
- 2 The locus minoris resistentiae is in the subcutaneous vessels more than in the cutaneous
- 3 The contention that bacteria are probably the cause of hemorrhage he disproves by the fact that in phlyctenosis streptogenes, the streptococci are found in the capillaries, the same is true of the disease known as pustulosis staphylococci, but they cause necrosis of the endothelium only and not bleeding
- 4 In hyaline degeneration of the endothelium he says that it produces thickened walls but no fragility, therefore there is no chance for rupture

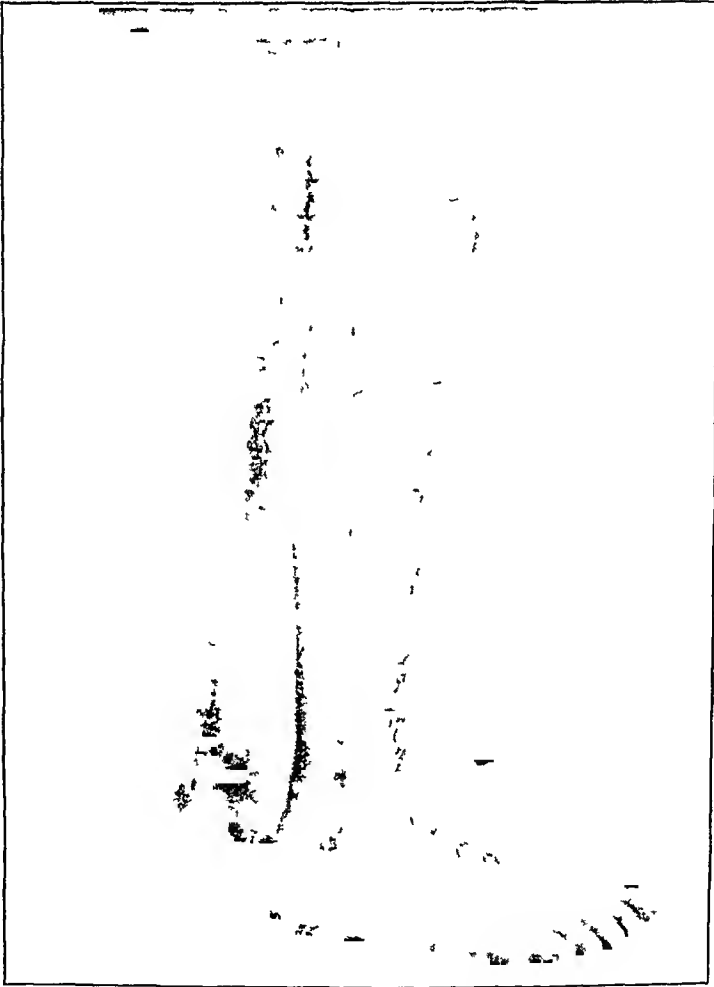


Fig 2—Purpuric areas on legs of patient G I (Case 3)

5 He also tries to disprove the theory of Rayer, who found purpura after the right iliac vein was thrombosed, with the argument that in varicose veins the tone of the vessel helps dilatation, and never rupture

6 The only condition of purpura in which he recognizes the complete degeneration of the vessel as being its immediate cause is in the vessel paralysis or antemortem vascular changes, where the vessel yields and ruptures

Pratt, in Osler's *Modern Medicine*, among the many causes of purpura which we have already discovered, quotes a good many authorities

who have worked on this subject from the serological point of view. This work has been done mainly at the Johns Hopkins Hospital. According to the author the probable additional causes for purpura may be a lack of fibrinogen in the blood, or a fibrinolysin, because in many cases of purpura one finds the coagulation time delayed. The authors also found that in the case of any fatty degeneration of the liver (the yellow atrophy of the liver) the cells are destroyed, lack of fibrinogen is the result of these changes, thus aiding in producing this condition. The same is true of phosphorus poisoning, which acts similarly on the liver.

They also found the blood platelets diminished in purpura, and that there is usually a leukocytosis present. Unna repudiates this very strongly.

Ewing<sup>8</sup> claims that bacteria are found in some cases in the blood and these are isolated, as for instance Letzeuck's *Bacillus purpura*, which is in turn produced in animals, *Streptococcus pyogenes* has been isolated in typical cases by Hanot and Luzet, Widal, Therese and Guarnieri, *Staphylococcus pyogenes aureus* has been isolated by Lebreton, Litton, Fischl, Adler, Lewis and Librestini, the *Pneumococcus lanceolatus* by Clause and Claudi.

Changes in blood were found by Carrere and Gilbert, who reported a mild case having 3,350,000 red cells, while in more severe cases the diminishing number is greater, the hemoglobin index was subnormal. They also found a leukocytosis.

Hayem<sup>9</sup> claims that there exists a retardation of the coagulation time, and a reduction of blood plates.

Ewing states that the clotting appeared to be abnormally rapid, as in the course of an hour the specimen in the hematocytometer, diluted 1:100 with 0.6 per cent salt solution, became jelly-like. Grawitz has also found an increase in the coagulability of the blood in these cases, after repeated hemorrhages, but red cells were found rapidly diminishing, and leukocytes were normal or reduced in numbers.

Stelwagon<sup>10</sup> agrees with Ewing in saying that there exists a mechanico-bacterio-toxic and chemical cause of purpura. He maintains that there must be a hyperemia and rupture or diapedesis of the vessel to produce purpura.

Hayem, who claims that the retardation of coagulability of the blood is due to the diminution of platelets, and to their destruction brought about by intestinal toxemia, this phenomenon is also found in cachectic conditions, such as leukemia, nephritis, carcinoma and "tuber-

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<sup>8</sup> Ewing's Clinical Pathology of the Blood, 1903.

<sup>9</sup> Hayem. Quoted in Am Jour Med Sc, 1911 vol. III, by Mathew and Carpenter in Purpura Hemorrhagica.

<sup>10</sup> Stelwagon's Diseases of the Skin Ed 7, 1915.



culosis with purpura, the toxic substances of which are likely to produce profound changes in the blood, which lead to the rapid disintegration of the vessel wall, or to the slower hyaline or fatty degeneration"

John M. Cruice<sup>11</sup> says

Bensaude and Rivet think that purpura is not infrequently associated with tuberculosis. Of their thirty-five cases of chronic purpura hemorrhagica, seven occurred in individuals undoubtedly tuberculous, and in individuals probably tuberculous. They say that in the presence of a purpura, particularly in the recurring or chronic form, when the cause is not apparent, the clinician should by all means in his power, look for some chronic tuberculous lesion, either of the lungs, of the glands, or some other part of the body.

Brown says that purpura hemorrhagica rarely occurs in tuberculosis. In the last 1,000 cases at the Adirondack Cottage Sanitarium but three cases have occurred. This corresponds closely to my figures. Out of 1,626 ward patients at the Phipps Institute I was able to find only eight cases of purpura. Mackenzie, in 200 cases of purpura, found it associated with tuberculosis only four times. Pratt in 258 cases of purpura, both primary and secondary, found it associated with tuberculosis seven times.

Grenit attributes the cause of purpura to one of the following conditions:

- 1 Hepatic lesion
- 2 Nervous injury
- 3 Intoxication of some sort
- 4 Bacteria
- 5 Blood changes

but offers no discussion or explanation thereof.

Howell<sup>12</sup> states that he found a great diminution in the prothrombin, as in hemophilia, which retards coagulation and does not affect the antithrombin substance.

In thrombosed vessels the prothrombin is not affected but the antithrombin is diminished. In purpura hemorrhagica neither is affected.

Gaucher<sup>13</sup> claims as follows:

1 Infective secondary purpura is met with in the course of infective diseases such as variola, scarlatina, measles, intermittent fever, pyemia, puerperal infection, ulcerative endocarditis, acute tuberculosis (of which purpura may be a premonitory phenomenon), diphtheria, enteric fever, typhus, plague, malignant jaundice, pneumonia, cerebrospinal meningitis, infective tonsillitis and gonorrhea.

2 Toxic purpura is due to the absorption of certain protein substances, but a certain predisposition is necessary for this to occur.

Herbert French<sup>14</sup> maintains that "General tuberculosis is not a common cause of purpura, and yet in a few instances extensive purpura has

11 Cruice, John M. The Incidence of Purpura in the Course of Chronic Tuberculosis, *Am Jour Med Sc*, 1912, cxlv, 875.

12 Howell, W. H. Condition of Blood in Hemophilia, Thrombosis and Purpura, *THE ARCHIVES INT MED*, 1914, xiii, 76, absts in *Jour Am Med Assn*, 1914, lxii, 488.

13 Gaucher. Diseases of the Skin.

14 French, Herbert. An Index of Differential Diagnosis of Main Symptoms, William Wood & Co, New York.

been the first, and, for the time being, the only, symptom of an obscure illness which has ultimately turned out to be general tuberculosis. The patient has generally been a child, and the diagnosis has only been possible when the course of the case has been watched."

The following are the three cases which have come under observation within the last eight months. It is useless to say that they can be taken as a criterion to prove anything regarding the cause of pathogenesis of purpura, but they do show us that there is a definite inter-relationship between it and tuberculosis, and possibly give a clue to its etiology.

#### REPORT OF CASES

CASE 1—W S, aged 29, carpenter, Russian

The condition of the lungs Nov 16, 1914, was as follows

Right lung Dulness of both superior and middle lobes anteriorly and posteriorly, with large cavity over the same area, and moist râles all over

Left lung Dulness of both superior and middle lobes anteriorly and posteriorly, with amphoric breathing over the same area, and moist râles all over

From Dec 12 to Dec 29, 1914, the patient showed the following additional symptoms: edema over the ankles, marked dyspnea, cyanosis, slight epistaxis, abdominal pain and nausea

Dec 29, 1914, patient was awake until 3 o'clock in the morning, felt nauseated and vomited coffee-colored material three times. Bowels also moved three times during the night, stools were loose and watery in consistence. Patient vomited twice in the morning, a dark greenish fluid. On examination patient was found markedly prostrated. He did not complain of anything except marked weakness. Hemorrhagic spots covered both legs, over the anterior and lateral surfaces and posteriorly. Similar hemorrhagic outlines covered the upper third of both legs and lower third of both thighs. Some spots were also seen over parts of the buttocks. They were also distributed over the inner surfaces of both forearms and upward to the midpoint of the arms. These hemorrhagic spots were confluent and covered areas 4 to 6 inches in length and about 3 inches in width. They were of a deep bluish-red hue.

The mucous membranes and the conjunctivae were negative. The chest findings were the same as on previous examinations.

From Dec 29, 1914, to Jan 1, 1915, the patient persistently vomited dark greenish fluid. The greater curvature of the stomach was low, reaching midway between the pubes and umbilicus, and a splashing fluid was readily made out.

From Jan 1 to Jan 10, 1915, the patient complained for the first time of pain in the right knee, and in both elbow joints. The purpuric rash became paler, and gradually disappeared. The face was puffed.

From Jan 10 to Jan 14, 1915, the puffiness grew more marked, the purpuric rash reappeared over the legs. Examination of the urine revealed an excessive amount of albumin, and numerous casts of all kinds, including a few waxy casts, and many cylindroids.

From Jan 14 to Jan 16, 1915, the purpuric rash gradually disappeared again. The patient became very dyspneic and cyanosed, the pulse was rapid, feeble and irregular in force. The heart beat was irregular, and a blowing

systolic murmur was heard at the apex, which was not transmitted. The second pulmonic was accentuated.

Jan 16, 1915, the patient's general condition was somewhat improved. He complained of hunger, and wished to be out of bed, but dyspnea was still marked. The pulse was small, feeble and irregular. The puffiness of face subsided. There was no edema of the extremities. At 11 15 a m the patient sat up, but suddenly fell back and expired.

The blood on repeated examinations showed an average leukocyte count of 8,000 to 12,000, red cells of 4,500,000 to 5,000,000, and neutrophils 70 per cent. The hemoglobin was an average of 75 per cent. The blood culture revealed nothing.

CASE 2—S. A., aged 28, draughtsman, American.

The condition of the lungs was as follows:

Right lung. Dulness anteriorly from apex to third interspace, posteriorly from apex to sixth spinal vertebra, also one stripe at the base. On auscultation was found bronchial breathing, with moist râles from apex to third interspace anteriorly, posteriorly bronchial breathing, with moist râles from apex to sixth vertebral spine, below that there was feeble breathing.

Left lung. There were crackles all over anteriorly, posteriorly there was dulness over the supraspinous fossa, and feeble breathing could be heard to the fifth vertebra. Below that there was hyperresonance.

An attempted artificial pneumothorax on the right side was without the desired result. May 8, 1915, the patient developed marked edema of the right lower extremity, which lasted for three days, and which was accompanied by pain in the leg. The third day his left foot became markedly edematous. There were no signs of abdominal fluid or enlargement of liver or spleen. On examination the patient showed signs of a spontaneous pneumothorax on the right side, with signs of the heart being pushed over to the left.

The roentgenogram showed that there was apparently a pneumothorax occupying the entire right thoracic cavity, pushing the collapsed right lung, as well as the mediastinum, completely to the left side.

About the left side nothing definite could be said, as it was markedly compressed and obscured by the mediastinum.

May 29, 1915, the patient was very dyspneic, showed pronounced cyanosis over the extremities, and complained of pain in swallowing. On examination evidence of fluid could be elicited at the base of the right chest, and 33 ounces of thin, turbid fluid, greenish in color, was obtained.

June 1, 1915, the general condition of the patient was very poor. There was tenderness all over the abdomen, especially over the liver, which was very large, and could be palpated as far as the umbilicus. He had also edema of the right lower extremity. His elbow and knee joints were tender. The patient showed a purpuric rash over the sacral region, over the right clavicle, anteriorly and posteriorly, over the right supraspinous fossa, and over the anterior portion of the right leg. These purpuric spots were of a deep bluish hue, which did not disappear on pressure, and which covered areas about 3 to 5 inches in length and 3 inches in width.

On five successive urinary examinations, before and after the appearance of the purpuric rash, no albumin could be found.

On two successive blood counts, before and after the appearance of the rash, the patient had an average of hemoglobin of 65 per cent, red blood cells, 5,000,000, white blood cells, 6,000, polymorphonuclear cells, 84 per cent, small and large mononuclear cells, 16 per cent. The blood culture was found negative, and no bacilli were found in the blood.

CASE 3—G I, aged 38, tailor, Russian

The lung condition on admission was as follows

Feb 18, 1915, the right lung showed dulness over two upper lobes, anteriorly and posteriorly, with bronchovesicular breathing and moist râles, below that the note was hyperresonant

The left lung showed dulness of the entire side, anteriorly and posteriorly, with bronchial breathing and moist râles all over

April 7, 1915, the physical examination and fluoroscope showed symptoms and signs of complete right-sided pneumothorax, absent breath sound all over, except the upper third posteriorly, and orthopnea

On inquiry the history given by the patient tells of a sudden onset at 10 30 p m, April 5, 1915

May 8, 1915, the patient developed a purpuric rash over the extensor and flexor surfaces of the right arm, up to the elbow, and a similar condition on the extensor surface of the left thigh The next day the patient had a swelling of the right wrist, followed by vomiting of bile-colored mucus This vomiting lasted for three days The patient also had diarrhea and blood-tinged stool He also developed edema of both feet This condition remained unchanged until May 23, 1915, when the patient developed edema of lower extremities The purpuric rash on the lower extremities became more confluent, and he complained of pain in the knee joint, and also dyspnea on slight exertion

From Jan 18 to May 5, 1915, patient's urine showed the presence of albumin, hyaline, finely granular and epithelial casts

The blood picture before and after the onset of purpura showed that the systolic blood pressure averaged 106, and diastolic, 80, hemoglobin, 80 per cent, red blood cells, 4,450,000, white blood cells, 8,000, neutrophils, 75 per cent, small and large lymphocytes, 29 per cent Blood culture negative Coagulation time normal

#### CONCLUSION

Clinically expressed, the purpura observed in our three cases can be grouped in the same category with the condition known as peliosis rheumatica of Schoenlein All the patients complained of pain in the joints, which came on suddenly and simultaneously with the onset of the rash, and all the cutaneous hemorrhages were of the simple type, with the exception of a single case, in which the patient's stool showed traces of blood—evidently suggesting purpura hemorrhagica proper

Pathologically, we cannot put our cases in one distinct type of purpura, because they show characteristics common to all the classes

For instance, blood cultures were found negative for bacteria The red blood cells averaged from 4,500,000 to 5,000,000, white blood cells averaged 6,000, neutrophils 80 per cent, hemoglobin averaged 65 per cent, blood platelets were normal The time of coagulation was normal They all had edema of the extremities, all had diarrhea, one, in addition, showed albumin and casts in his urine, another had bloody stools, they were all prostrated, all manifested symptoms of spontaneous pneumothorax, and all showed a rash on similar locations, almost similarly distributed all were confluent and did not disappear on pressure

Therefore, the following are the facts which explain our claim

1 According to Muir, though not found in our cases, the tubercle bacilli form colonies in the cutaneous vessels, where they act as an irritant

2 The secreted or excreted tuberculous toxins contribute to the necrosis of the cutaneous vessels

3 The serum extravasated into the dependent portions, either by pressure exerted on some vein or lymphatic vessel, or when this is directly due to nephritis, produces in turn a pressure on the cutaneous vessels, which may act as a mechanical factor

4 In the later stages of pulmonary tuberculosis the viscera may undergo either hyaline, amyloid or fatty degeneration, which aids in disintegrating the endothelial cells of the blood vessels, producing necrosis of the endothelium, and rupture, the fibrinogen-forming cells in the liver are also destroyed by the morbid process, thereby producing diminution in the viscosity of the blood, and also delaying its coagulation

To sum up The blood picture found in our three cases does not correspond with that found by the various authors quoted in our review of the subject

But we did find, in these three cases, sufficient factors to warrant us in claiming that there is a relationship between purpura and tuberculosis

They all showed the symptoms of intestinal toxemia, of amyloid degeneration, of the mechanical factors, and of general toxemia

As we have seen in our review, one writer would lay stress on one factor as being the cause of purpura, another would find a different cause In our cases we found a few causes which strengthen our belief that purpura can be found more often in tuberculosis than has been reported

I am indebted to Dr M Fishberg and Dr S Wachsmann for their aid, encouragement and courtesy in offering their material

# REMARKS ON *B. WELCHII* IN THE STOOLS OF PELLAGRINS<sup>\*</sup>

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The object of this paper is to call attention to the presence of abnormally large numbers of organisms belonging to the *B. Welchii* group, which have been found in the stools of pellagrins and to inquire whether this organism may not possibly bear a causal relationship to the disease.

*B. Welchii* has been described by various investigators since first described by Welch and Nuttall<sup>1</sup> in 1892 as *B. aerogenes capsulatus*.

For a complete description of the organism, with bibliography, reference may be made to the excellent monograph by Simonds.<sup>2</sup>

The characteristics of *B. aerogenes capsulatus* (*B. Welchii*) are as follows. It is a large gram-positive, nonmotile, anaerobic bacillus, producing spores under certain conditions. It is capable of fermenting nearly all sugars, and starch, and grows best on mediums containing these substances. In direct smears from lesions caused by it a capsule may be demonstrated. It coagulates and ferments milk with the production of butyric acid, and produces butyric acid from all sugars and starch. It is practically ubiquitous in distribution, having been found in the intestinal tract of domestic animals, birds and man, in the soil, water and air and in meat, fish, milk, cheese and other foodstuffs. The pathogenicity for man is limited. The resistance to conditions unfavorable to its growth is slight. Free oxygen and organic acids in a strength of 4 per cent. cause cultures to die quickly. The spores withstand a temperature of 80 C. for fifteen minutes but are usually destroyed by boiling for fifteen minutes. Simonds found the production of agglutinins in rabbits difficult.

The chief point of interest in connection with *B. Welchii* is that while it is recognized as a common inhabitant of the human intestinal tract, certain dietetic errors may cause it to assume a rôle of pathologic importance.

Growth by cultural methods in the absence of sugar is extremely difficult. Similarly, as pointed out by Kendall and Day,<sup>3</sup> *B. Welchii* is of no pathologic importance in the intestinal tract unless there is

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\* Submitted for publication Nov. 23, 1915.

<sup>\*</sup> From the Department of Pathology, Northwestern University Medical School.

<sup>1</sup> Welch, W. H., and Nuttall, G. H. F. Bull. Johns Hopkins Hosp., 1892, 111, 81.

<sup>2</sup> Simonds, J. P. Monograph 5, Rockefeller Institute of Medical Research.

present an excess of utilizable carbohydrates and a deficiency in organisms of the lactic acid group, which produce conditions inimical to its growth. These investigators in their work on children at the Boston Floating Hospital, found that the feeding of sugars in an intestinal infection by *B. Welchii* was contraindicated and rapidly caused an increase in the severity of the symptoms, the chief of which was diarrhea. By the withdrawal of sugars from the diet and the addition of lactic acid and lactic acid bacilli introduced in the form of buttermilk, the diarrhea stopped and *B. Welchii* in the stools decreased in number to normal.

In the early part of August, 1909, a large number of cases of pellagra were reported to the State Board of Health from the Peoria State Hospital at South Bartonville, Ill. The secretary of the board detailed me to assist in an investigation to be carried on in conjunction with one undertaken by the U. S. Army Medical Corps. The results of these investigations were published by the board in the Health Bulletin.<sup>3</sup> At that time *B. Welchii* was found in the mouths of some patients and in the stools of thirteen out of eighteen. The drinking water of the hospital was found to contain a gas-producing organism which, however, was lost in plating. This may have been *B. Welchii*. Conditions at the hospital at the time the water was examined were not favorable to the making of anaerobic cultures. No gas was produced by any of the organisms isolated by aerobic cultures.

In two cases of pellagra recently studied<sup>5</sup> an amount of fluid feces adhering to a straight platinum wire of 20 gauge immersed one-quarter inch produced stormy fermentation of milk in twelve hours after heating to 80 C. for fifteen minutes. This was due to the presence of *B. Welchii*.

McNeal and Allison<sup>6</sup> in a study on the bacteriology of the stools in pellagra reported the presence of *B. Welchii* in a number of cases. In one case in which the stools were examined during the acute manifestations of the disease they remark, "This would indicate the presence of *B. Welchii* in hundreds of thousands per milligram of feces." They also remark that the diagnosis of pellagra in this case is doubtful "as the discoloration on the hands gradually faded without desquamation." From personal observation I am of the opinion that this is not an unusual occurrence in pellagra. McNeal and Allison attached no

3 Kendall, A. I., and Day, A. A. Boston Med. and Surg. Jour., 1910, 1911, 1912.

4 Bulletin Illinois State Board of Health, August, October, and November, 1909.

5 Courtesy of Dr. Charles B. Read, Peoria, Ill.

6 Report of the Pellagra Commission of the State of Illinois, November, 1911, p. 55.

unusual significance to *B Welchii* as a possible cause of the diarrhea, so pronounced in pellagra

As above mentioned, Kendall and Day have reported that one of the essential conditions for the production of pathogenicity of *B Welchii* is a high carbohydrate diet. Hewes and Kendall<sup>7</sup> report investigations on diarrhea in adults which were characterized by the presence of large numbers of spores of *B Welchii*, which became worse on carbohydrate diet and rapidly improved on a pure protein and buttermilk diet.

It is notable in this connection that during the epidemic of pellagra the dietary of the Peoria State Hospital was reported to the Secretary of the State Board of Health as being very deficient in proteins and especially in proteins of animal origin. Conditions favorable to the growth of *B Welchii* were ideal.

The conclusions reached by Wussow and Grindley as the result of investigations on the dietaries of the state institutions, made for the pellagra commission were as follows:

Measured by the quantities consumed by a group of average patients fifty-three in number, for a period of seven days, the general diet supplied per man per day was 73.51 gm of protein, 444.34 gm carbohydrates, 55.77 gm fat, 2,568 calories of energy, and 23.23 gm of mineral matter, of which 1.07 gm was phosphorus. With the exception of protein and phosphorus these quantities are probably adequate.

They further conclude that since the protein intake "represents the average intake of a large number, some of whom were very likely receiving less than the average, an increase in the amount would seem desirable. A study of the distribution of the nutrients among the animal and vegetable foods shows that the diet is chiefly vegetable in nature, much more so than the average American dietary." This work was done at Peoria during the time indicated at the top of the fourth column of H. Douglas Singer's table, to be found in the same report, and herewith quoted, and therefore does not indicate the true conditions during the time of the epidemic.

Singer remarks "without wishing to draw any conclusions as to cause and effect" that "the number of cases of pellagra diminished at Peoria and Dunning coincidently with increased meat and have increased at Elgin with diminished meat."

The above observations were about to be submitted for publication when Goldberger, Waring and Willets<sup>8</sup> published the results of their investigations.

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<sup>7</sup> Hewes, H. F., and Kendall, A. I. Boston Med and Surg Jour., 1912, clxvi, 75.

<sup>8</sup> Goldberger, Joseph, Waring, C. H., and Willets, D. G. Pub Health Rep., Oct 22, 1915, p. 3117.



Their work is so important that it demands critical analysis. Commenting on the theory as to the communicability of pellagra, they observe that since nurses and attendants in institutions where pellagra is endemic do not acquire the disease although exposed to constant infection, the explanation of the phenomenon would be found in the difference in diet of the two groups of residents. They noted in one institution that meat or other animal protein food formed a relatively small part of the diet of those subject to pellagra, while the vegetable component was unusually large. Similar conditions were found at other institutions. In one of these seventy-nine cases of pellagra were observed during the spring and summer up to Sept 15, 1914. In a second institution 130 cases were observed during the same period.

AVERAGE DAILY AMOUNT OF MEAT\* IN OUNCES SUPPLIED TO EACH INDIVIDUAL INCLUDING BOTH PATIENTS AND EMPLOYEES† (SINGER)

	July 1907 to July 1908	July 1908 to July 1909	July 1909 to July 1910	July 1910 to July 1911	Average
Peoria	5.3	5.8	5.9	8.2	6.3
Anna	11.3	10.9	10.6	9.8	10.65
Chester	6.4	5.0	4.5	6.4	5.6
Elgin	7.1	7.7	6.9	5.9	6.9
Jacksonville	10.6	10.9	11.3	10.5	10.8
Kankakee	8.7	7.8	8.0	8.2	8.2
Watertown	8.2	7.9	8.4	8.3	8.2
Dunning	6.5	6.5	6.6	7.5	6.8

\* Uncooked and undressed

† Employees are fewer in number but receive relatively larger amounts than patients

Hygienic and sanitary conditions at both institutions were poor, but were not changed. September 15 the diet of the inmates was improved by the addition of milk, eggs, meats and leguminous vegetables. The carbohydrate element was at the same time considerably diminished. It is to be noted that in April, 1915, buttermilk was added to the diet. They give no reason for this addition, which at first was furnished on alternate days to inmates over 12 years of age, later when a sufficient supply was obtainable it was served daily to all.

The results obtained were as follows

In the first institution, of the 79 cases, 67 were under observation for one year. In none of them was there a recurrence of the disease. In the second institution, of the 130 cases, 105 were under observation for one year. In 1 case only was there a recurrence. None of the

nonpellagrin residents numbering, respectively, 99 and 69, developed the disease.

At the Georgia State Sanitarium, 72 pellagrins (36 colored and 36 white) out of 80 selected cases were under observation from not later than Dec 31, 1914, up to Oct 1, 1915. As at the other institutions, an increase was made in the protein food, syrup was entirely excluded and buttermilk was given twice daily. None of this group of 72 patients showed evidence of a recurrence at the end of the experiment.

During this period fifteen of thirty-two female pellagrins developed recurrences.

Goldberger and Wheeler<sup>9</sup> further to test the effect of diet in pellagra undertook to produce the disease experimentally in a group of non-pellagrous convicts. Of eleven volunteers who were fed for five months on a diet entirely free of animal protein, six developed a typical dermatitis and mild but distinct nervous and gastro-intestinal symptoms. It is to be regretted that these excellent studies did not include a study of the bacteriological flora of the feces before and after placing the patients on the test diet. The theory that *B. Welchii* alone or in symbiosis with another organism in the presence of an excess of carbohydrates, by the production either of butyric acid or a toxin, and their subsequent absorption may produce pellagra, is an attractive one. It harmonizes well with the infectious, toxic, and nutritional theories. It explains seasonal variations and the relation of poverty to pellagra. Poverty is usually associated with unhygienic, unsanitary living conditions, a high carbohydrate diet and a low animal protein diet as pointed out by Sydenstricker.<sup>10</sup>

#### SUMMARY

1 *B. Welchii* has been found with marked regularity in the stools of pellagrins in numbers greater than normal.

2 These pellagrins were on a dietary composed principally of vegetable foods high in carbohydrates.

3 The diet was extremely low in protein and especially in protein of animal origin.

4 Diarrhea is one of the most constant symptoms of the disease known as pellagra.

5 *B. Welchii* has been found to produce severe diarrhea in children and adults in the presence of a high carbohydrate diet.

6 The diarrhea caused by *B. Welchii* can be cured by a protein diet and buttermilk.

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<sup>9</sup> Goldberger, Joseph, and Wheeler, G. A. Pub. Health Rep., Nov. 12, 1915, p. 3336.

<sup>10</sup> Sydenstricker. Pub. Health Rep., Oct. 22, 1915, p. 3182.

7 Goldberger has prevented pellagra by the addition of proteins and buttermilk to the diet, and has experimentally caused pellagra by means of a pure carbohydrate diet

8 Whether *B. Welchii* was present in the stools of Goldberger's cases in greatly increased numbers is not known

The above facts by no means prove that *B. Welchii* is the direct or sole cause of pellagra, but their coincidence is sufficiently significant to justify further investigation

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#### CORRECTION

Attention is called to the following corrections in article by Drs Harold Schwartz and Caroline McGill in THE ARCHIVES for January, 1916

Under Table 2, giving the normals of various authors, the values given refer to urea nitrogen, with the exception of the figures given by Rowntree and Fitz, Schondorff, Farr and Austin (0.43), Widal, Picard, Weill and Vallery-Radot, which refer to urea

In the subject matter, reference to Tileston and Comfort, and Folin and Denis, refer to urea nitrogen

Conclusion No. 1, the word "fasting" should be omitted

## STUDIES OF EDEMA IN PNEUMONIA

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It has long been known that acute infectious diseases may be accompanied by edema of the skin and subcutaneous tissues. While in some cases of pneumonia this edema may be sufficiently well marked to cause pitting on pressure, in the majority of cases, such evidence is not present, notwithstanding definite water retention. It would be expected, following the explanation of Fischer,<sup>1</sup> that edema would be an almost constant accompaniment of pneumonia, for we have here a disease in which several factors,<sup>2</sup> as the increase in ammonia output, the decreased carbon dioxide content of the blood, etc., make it very probable that there is an interference with oxidative processes of the organism.

According to Fischer the inhibition of oxidation, with the concomitant increase in acidity, is of great importance in the production of edema. That this edema may occur and not be appreciated is not surprising, when we remember the great amount of water retention which may occur before it becomes manifest as palpable edema.

By means of Schade's elastometer,<sup>3</sup> an instrument described in a previous communication, the question of edema in pneumonia has been studied. With this instrument it is possible to detect edemas not appreciable by the palpating finger. In a series of ten cases of pneumonia we have found with the elastometer the presence of slight or moderate edema in every case.

This edema, shown in the elastometric reading by the character of the curve and the deficient return of the curve to the base line, seems to be most marked during the height of the disease.

After the crisis, the curve has a tendency to return very slowly to normal. Occasionally, this return to normal is nearly complete soon

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\* Submitted for publication Dec 11, 1915

\* From the Otho S A Sprague Memorial Institute Laboratory of the Children's Memorial Hospital

1 Fischer, Martin H. Edema and Nephritis. New York 1915

2 Peabody, Francis W. Jour Exper Med, 1912 211, 701

3 Schade, H. Ztschr f exper Path u Therap, 1912 21, 369

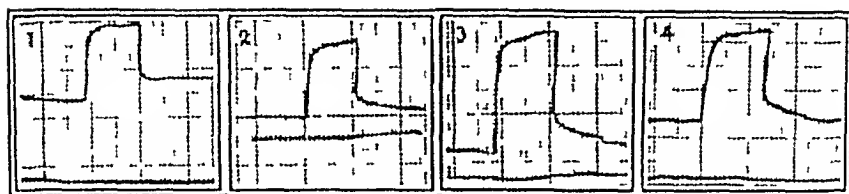


Fig 1—Curve 1 is a reading taken twelve hours after crisis. The subsequent readings illustrate the gradual but complete return to normal elasticity, the last reading being taken two weeks after crisis.

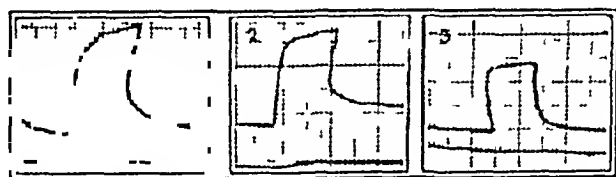


Fig 2—Curve 1, taken just before crisis, shows a very slight loss of elasticity. The second reading shows a greater loss. The last reading shows a complete return to normal.

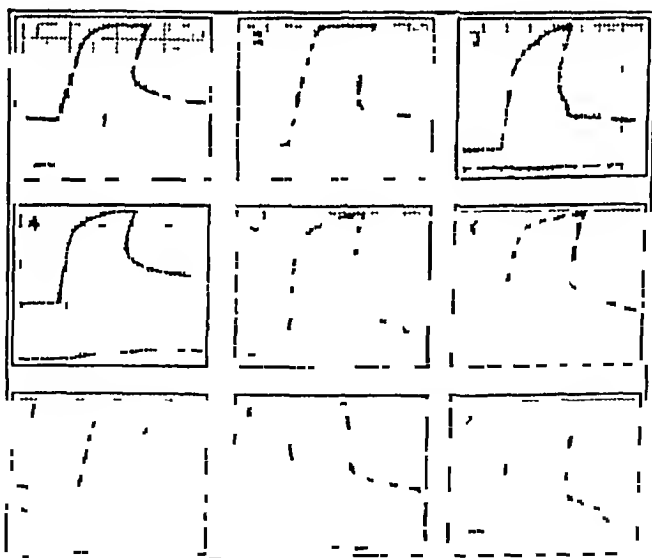


Fig 3—This figure illustrates the marked changes in tissue turgor which may occur in young children, following the infectious diseases. The patient on whom these readings were taken, was admitted to the hospital on the fifth day of a lobar pneumonia complicated by a double suppurative otitis media. Curve 1 is a reading taken on the day of admission. Curves 2 and 3 were taken during the height of the fever. The last six readings were taken during convalescence, the patient remaining in the hospital pending the selection of a suitable home by the Social Service Department. Clinically the only apparent delay in convalescence was a very noticeable lack of energy in the patient. The pronounced loss of elasticity and its persistent character is quite marked, the elasticity curve approximating normal six weeks after crisis.

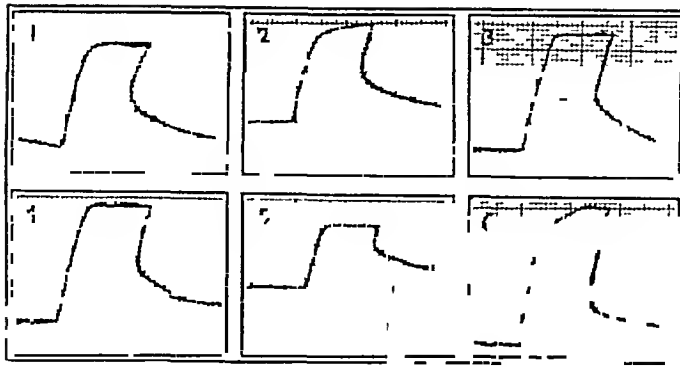


Fig 4—The readings in this case are further illustrations of the changes in elasticity which occur in young children. The patient was 3 years old. The first two readings were taken during the height of the disease. Curve 3 on the day of crisis. The elasticity loss persists after crisis.

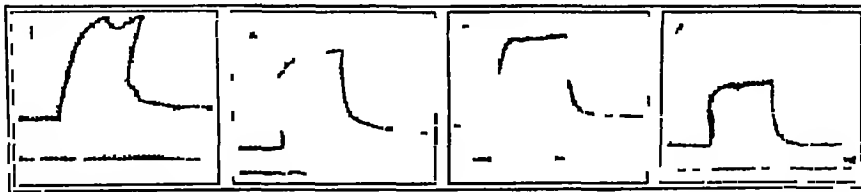


Fig 5—This figure shows a series of readings exhibiting a complete return to normal. The first two curves were obtained before crisis, the last two after crisis.

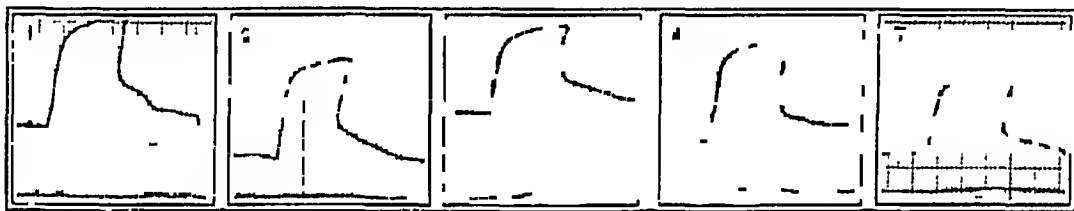


Fig 6—This shows variations in the elasticity curve taken during the course of a lobar pneumonia, complicated by an otitis media and furunculosis of the auditory canal. The clinical chart of the patient showed a similar irregularity in the temperature curve, which may bear some relationship to the fluctuations noted.

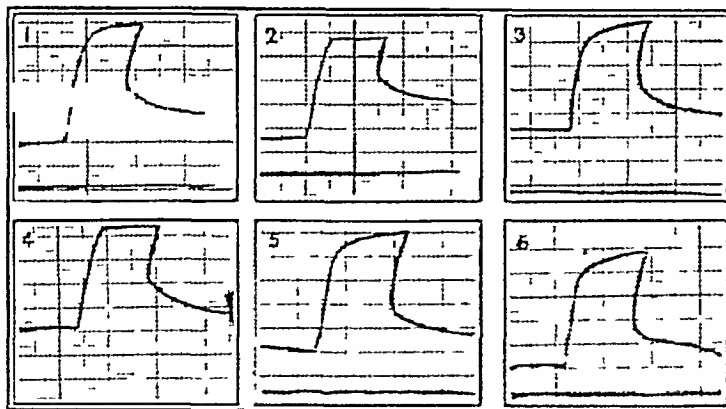
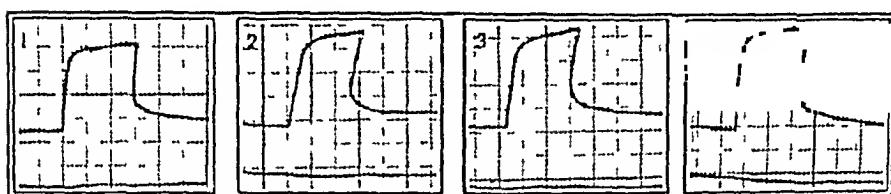
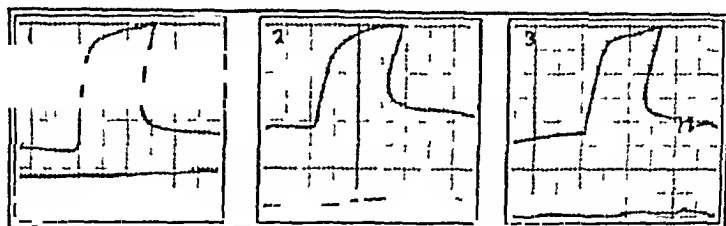


Fig 7—This illustrates an improvement in the elasticity curve immediately following crisis. The successive curves showing a gradual return to normal. The first two readings were taken before crisis. Curves 3 to 6 after crisis.

after crisis, while in other cases, there persists slight elasticity loss long after apparent convalescence. In some instances this persistent loss may be associated with complications. What factors influence such deficient return to normal, and their significance, we are not able, at present, to say.



Figs 8 and 9—Further examples of slow improvement after crisis. The first curve in each of these figures was taken before crisis, the other curves after crisis had occurred.

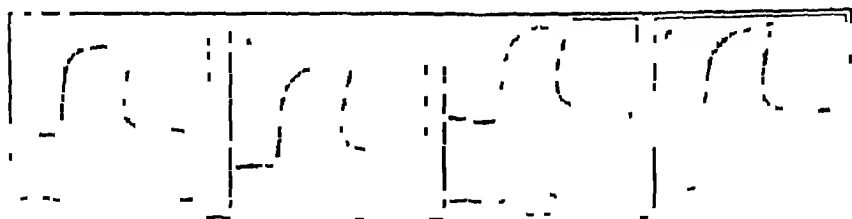


Fig 10—Curves 1 and 2 in this figure taken during the height of a lobar pneumonia show a slight loss of elasticity. On May 6, the temperature had reached normal by lysis. The reading taken at this time shows practically normal elasticity. Six days later, a reading shows a greater loss of elasticity than had been noted even during the height of the fever. Twelve hours after this reading was taken, the patient exhibited a marked characteristic rash of scarlet fever. Though further readings were not taken, on account of the necessary isolation of the patient, the striking change in the character of the curve suggests the possibility that associated with certain acute infectious diseases, earlier and profounder changes in tissue turgor may occur than has been heretofore thought.

The elastometric curves given in the text were all obtained at the wrist in patients admitted to the Children's Memorial Hospital with lobar pneumonia. In none of these cases was there any palpable edema. On account of the difficulty of working with children, some of the curves are not perfect. Nevertheless, the variations noted are sufficiently well marked for our study.

## THE RELATION OF CHLORIDS TO EDEMA IN PNEUMONIA

The retention of chlorids in pneumonia has been studied by many observers, and recently, McLean,<sup>4</sup> using his new method of chlorin determination,<sup>5</sup> has shown that failure to excrete chlorin in pneumonia is associated with a lowered concentration of chlorids in the plasma, and that excretion begins at the time this concentration increases. That this increase is usually more marked than can be accounted for by the increased diet, has been noted by various observers. Numerous studies have been made to determine the point at which this retained chlorid is stored.<sup>6</sup>

## CHLORIN DETERMINATIONS IN URINE IN PNEUMONIA

Date	Day of Disease	Clinical Observations	Urinalysis				Chlorid Per Cent Blood Serum	Number of Curve
			Cl, Per Cent	Cl, Gm	Sp Gr	Output in 24 Hrs, c c		
1915 1/24	7th	Temp 102 103.5	0.28	0.7	1.020	250	0.53	Fig 3
1/27	10th	Temp 102 104	0.16	0.44	1.018	275		
2/ 2	16th	Third day normal					0.57	
2/18	32d	Condition normal	0.67	3.9	1.015	575	0.61	
2/15	7th	Temp 102 104	0.024	0.08	1.023	335	0.53	Fig 5
2/19	11th	Improving					0.53	
2/21	13th	Improving	1.28	6.0		470	0.60	
3/ 6	5th	Temp 102-104	0.69	1.04	1.018	150	0.54	Fig 6
3/14	13th	Temp 98 101	0.33	1.51		457	0.57	
3/22	21st	Temp 99 104	0.23	1.08	1.011	470	0.64	
2/27	6th	Temp 103-104	Trace		1.010	475	0.51	Fig 7
3/ 4	11th	Temp 99 100	Trace		1.013	90	0.57	
3/10	17th	Condition normal	0.63	3.5	1.010	570	0.56	
4/18	6th	Temp 102-104	0.2	1.4	1.015	700	0.52	Fig 8
4/21	9th	Normal	0.59	1.9	1.018	320	0.57	
4/25	13th	Normal	1.0	5.6	1.020	560	0.61	
4/21	5th	Temp 102 104	0.065	0.3	1.019	462	0.54	Fig 9
4/25	9th	Temp 98 99.5	0.04	0.07	1.015	185	0.55	
4/27	11th	Temp 98 101	0.18	1.65	1.009	920	0.62	
5/ 6	20th	Normal.	0.97	7.1	1.015	740	0.65	
4/30	3th	Temp 102 103	0.1	0.35	1.012	320	0.52	Fig 10
5/ 2	7th	Temp 101 104	0.22	1.9	1.017	450	0.59	
5/ 7	12th	Normal*	0.07	0.47	1.012	675	0.51	

\* Fever the next day, scarlet fever six days later

4 McLean Franklin C Jour Exper Med, 1915, xxii, 212, *ibid*, 366

5 McLean F C and Van Slyke, D D Jour Biol Chem, 1915, xxi, 361.

6 Peabody, Francis W Jour Exper Med, 1913, xii, 71



Having invariably found the presence of some edema in pneumonia by means of the elastometer, we undertook to correlate, if possible, these findings with chlorid determinations of the blood and urine. The difficulty of obtaining blood and the comparative infrequency of uncomplicated lobar pneumonia in the children at our disposal, made the number of our observations small.

For the determinations of chlorids in the blood, McLean's method was used, for urine, Volhard or Dehn's modification of the Volhard method.

In twenty-two observations of the chlorids in the blood serum, made in seven cases of lobar pneumonia, our results confirm those of McLean regarding the diminished concentration of chlorin in the plasma during the height of the fever, with increased concentration after crisis.

Of all these patients, elastometric determinations are given in the text figures. While the increased concentration of NaCl in the blood occurs almost immediately after crisis, there does not seem to be a corresponding change in the elasticity of the tissues, as determined on the wrist by the elastometer. The return to a normal concentration of NaCl in the blood serum usually occurs long before the elasticity curve has reached a normal state.

# HYPOGLYCEMIA AND PROGRESSIVE MUSCULAR DYSTROPHY <sup>1</sup>

R H McCRUDDEN, M D, AND C S SARGENT, S B  
BOSTON

We recently made urine and blood examinations in a typical case of progressive muscular dystrophy which was being studied clinically by Drs Goldthwait and Spear of Boston. The clinical findings are to be made the subject of a separate report, but the chemical findings seem well worth recording, even though they represent the data from but one case, since, if confirmed in other cases, they constitute a distinct contribution to our knowledge of carbohydrate metabolism. They are, therefore, published in the hope that similar examinations will be made by any other investigators who may observe a case of this uncommon disease.

## THE OBSERVATIONS

The patient was a man 33 years of age who showed no abnormalities except progressive muscular weakness. He was put on a constant diet, the urine was saved and examined quantitatively for calcium, magnesium, nitrogen, creatinin, creatin, uric acid, and ammonia, and the blood for glucose, creatinin, creatin, uric acid, cholesterol, and nonprotein nitrogen.

**DIET.** The patient was kept on a constant diet throughout the period during which specimens were taken. The diet was constant in calories, and in its nitrogen, fat, and carbohydrate content, and practically identical foodstuffs were given from day to day. In spite of this physiologic constancy, the food was served in a variety of forms to the patient. This constancy in composition combined with an appearance of variety constitutes a characteristic and very useful feature of our studies at this hospital. The results are obtained by cooperation of physician and dietitian, and we believe that an adoption of the principles applied will serve to clear up many dietetic difficulties. The principle to be recognized is that the physician must prescribe the diet, for he alone knows what is needed, but the physician rarely possesses the technical knowledge necessary for putting his diet into palatable form and for giving it variety, for this he must call on the dietitian. The relation of physician and dietitian in this respect resembles somewhat that of the physician and pharmacist with respect to medicines. For convenience of explanation, the complete carrying out of the process may be divided into four steps.

1 After deciding on the approximate diet to be given, preliminary observations of a day or two are made to find out the amount of food the patient can take and his dietetic idiosyncrasies.

2 A list of foodstuffs is then given to the dietitian from which a dietary of several days is to be made out. In this case the following list was prescribed for each twenty-four hours:

- 4 eggs (which may be replaced in part by cheese in the proportion of 1 ounce of cheese to 1 egg)
- 4 glasses of milk
- 600 gm of potato (which may be replaced in part by bread, spaghetti or rice in the proportion of 600 gm of potato = 240 gm bread = 150 gm rice)
- 60 gm butter

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\* Submitted for publication Dec 18, 1915

\* Laboratories of the Robert Brack Brigham Hospital

All these foodstuffs are fairly constant in composition and in caloric value, so that composition and caloric value can easily be calculated. In addition, once a day, a small amount of lettuce, cucumber, celery, and tomato, and a small amount of fruit, either raw or cooked, were allowed, these latter foodstuffs have very little caloric value, and contain but little protein, fat, and carbohydrate. Such a diet has the composition shown in Table 1.

TABLE 1—COMPOSITION OF EXPERIMENTAL DIET

	Grams	Protein	Fat	Carbo- hydrate	Calories
Four eggs	200	25	25		335
Four glasses milk	800	32	32	32	560
Potato	600			120	492
Butter	60		18		446
Total		57	105	152	1,833

3 The third step—a conference of physician and dietitian for examination and alteration of the first tentative dietary submitted by the dietitian—comes after the dietitian has studied the diet list. It sometimes happens that the diet prescribed can be improved in palatability or variety by slight alterations or additions which may or may not be permissible, depending on the exact purpose of the diet. In this particular case the diet was correct as first submitted.

4 The fourth step consists in the preparation of a dietary. For this patient we give three days' diet as examples in Tables 2, 3 and 4.

TABLE 2—SAMPLE DIET

Date			Eggs	Milk, c c	Potato, gm	Bread, gm	Butter, gm
19	Breakfast	Baked potato Toast, butter, milk Soft cooked egg	1	200	100	48	14
	Dinner	Bread, butter, milk		225		48	14
		Escalloped spaghetti with egg	1	55			12
		Lettuce (dressed) Ice cream	1	175			2 (oil)
	Supper	Soup Baked stuffed potato Bread, butter, milk Baked custard Grape fruit	$\frac{1}{4}$ $\frac{3}{4}$	200 20 225 100	200	56	14 14
Total for the day			4	1,200	300	152	70

Besides vegetables and fruits and small amounts of sugar, flour, condiments, etc

TABLE 3—SAMPLE DIET

Date			Eggs	Milk, c c	Potato, gm	Bread, gm	Butter, gm
20	Breakfast	Toast, butter, milk Cream toast Omelette	1	200 125		48 24	12 7
	Dinner	Asparagus soup Potato salad Baked stuffed egg Bread, butter, milk Lemon souffle Foam sauce	1 $\frac{3}{4}$ $\frac{1}{4}$	200 75 200	200	48	7 2 (oil) 7 12
	Supper	Cream of potato soup Croutons Toast, butter, milk Dropped egg on toast Cut fruit	1	200 200	100	32 24 24	9 14
	Total for the day		4	1,200	300	200	70

Besides vegetables and fruits and small amounts of sugar, flour, condiments, etc

TABLE 4—SAMPLE DIET

Date			Eggs	Milk, c c	Potato, gm	Bread, gm	Butter, gm
21	Breakfast	Toast, butter, milk Grape fruit Scrambled eggs	1	200 20		48	14 7
	Dinner	Soup, toast Baked potato Egg with tomato salad Bread, butter, milk Ice cream	1 1	200 200 160	200	24 24	2 (oil) 12
	Supper	Soup Potato souffle Bread, butter, milk Orange fluff	$\frac{1}{2}$ $\frac{1}{2}$	200 20 200	200	64	7 7 14
	Total for the day		4	1,200	400	160	70

Besides vegetables and fruits and small amounts of sugar flour condiments, etc

We intend to make this question of dietetics as carried out at the Robert B Brigham Hospital the subject of a separate publication and will not, therefore go into any more details here

URINE The greatest care was observed in collecting the twenty-four-hour quantities of urine. This is a difficult task. The number and kind of accidents and errors that can occur in quantitative urine collections can be appreciated only by one who has made a special study of this subject. It is our belief that the results of urine analysis offered in the literature without accompanying creatinin determinations as evidence of completeness of collection are of

little value. Belief in the good intentions and trustworthiness of the nurse cannot replace creatinin determinations. With the most expert assistance, and with the most rigid system, losses and unexplainable accidents will occur. Since we intend to make this whole question of urine collection the subject of a separate publication, we will not go into details here further than to say that three factors are essential:

- 1 Creatinin determinations
  - 2 The closest oversight possible, supplemented by complete detailed ward reports concerning all the happenings to the patient written and signed by the nurse in charge (such reports serve as the basis of an investigation and often give the clue to the cause of irregularities disclosed by creatinin determinations)
  - 3 Hearty cooperation in instituting, modifying, and carrying out the whole regime, the facilities for which are unusually good at this hospital.
- The patient was kept in a room about 20 feet from the laboratory. He was not allowed to leave the room and all visitors except the day and night nurse in charge excluded. The régime to be carried out was explained to the nurses both by myself and by the superintendent of nurses and minute type-written directions given besides. Urine was collected from 7 a m to 7 a m in special bottles containing a small amount of chloroform and alcoholic thymol solution as preservative. The bottle was kept right beside the patient's bedside in a box that was not unsightly or conspicuous. The urine secreted during the night was voided at 6 a m and then the bladder completely emptied again at 7 a m. In order to avoid losses at stool, the patient was instructed to void each time before emptying the bowels. He was asked each time by the nurse if he had remembered to void in advance and also if he had lost any urine while evacuating the bowels. Reports similar to the one in Table 5 were sent to the laboratory each day with the urine.

TABLE 5—SAMPLE OF DAILY REPORT

Patient's Name, Mr X		Date, Oct 22, 7 a m to Oct 23, 7 a m		
Urine	Feces	Food	Extra	Nurse
9 a m No urine 11 25 12 10 No urine	No stool 9 05 a m No stool No stool 12 15	7 30 a m, orange, egg on toast, butter and milk  12 30 p m, potato soup, cheese, salad, bread, butter, pota to with rice with egg sauce	No accident  No accident No accident No accident No accident No accident	
3 45	No stool	5 30, celery soup, bread, butter, milk, toma to, macaroni	No accident	7 30 a m to 7 30 p m Miss A E B
9 15 p m 3 15 a m 6 15 a m 7 00 a m	No stool No stool No stool No stool		No accident No accident No accident No accident	7 30 p m to 7 30 a m Miss M A B

The methods of analysis used were the following

URINE

Creatinin Folin's method, described in Journal of Biological Chemistry, 1914, xvii, 470

Creatin Folin's original method of heating the urine with HCl for three hours on the water bath and determining creatin plus creatinin

Uric Acid Folin and Denis's method described in Journal of Biological Chemistry, 1913, xiv, 97

Total Nitrogen Kjeldahl method

Calcium Magnesium McCrudden's method described in Journal of Biological Chemistry, 1911, x, 187

Blood  
Nonprotein Nitrogen Folin and Denis's method described in Journal of Biological Chemistry, 1912, xi, 529

Creatinin and Creatin Folin and Denis's method described in Journal of Biological Chemistry, 1913, xiii, 469

Glucose Lewis and Benedict's method described in Journal of Biological Chemistry, 1915, xx, 61, as modified by Myers and Fine in their pamphlet on Chemical Composition of the Blood in Health and Disease, New York, 1915

Uric Acid Folin and Denis's method, described in Journal of Biological Chemistry, 1913, xiii, 469

Cholesterol Authenrieth and Funk's method, described in Munchen med Wchnschr, 1913, lx, 1243

The urine and blood examinations were all made in duplicate, except the sugar determinations, which were made in triplicate

#### THE FINDINGS

*Urine Examinations*—The twenty-four-hour quantity of urine varied in amount from 920 to 1,450 c c, it was slightly acid to litmus paper. It was made up each day to 1,500 c c, examined qualitatively for sugar, acetone, diacetic acid and albumin (these compounds were always absent), and quantitatively for creatinin, creatin, uric acid ammonia, calcium, magnesium, and nitrogen. The results will be found in Table 6

TABLE 6—URINE EXAMINATIONS

Date	Volume, c c	Specific Gravity	Creat inin	Creat in	Uric Acid	Total Nitrogen	Ammonia Nitrogen	Cal cium	Magne sium
1	1,230	1.020	1.568	0.050	0.358	12.72	0.284	0.357	0.072
2	1,020	1.025	1.488	0.283	0.447	13.64	0.240	0.404	0.100
3	920	1.029	1.503	0.316	0.417	14.03	0.270	0.411	0.077
4	1,200	1.023	1.481	0.509	0.417	15.20		0.477	0.091
5	1,180	1.022	1.493	0.624	0.385	14.34			
6	1,230	1.023	1.486	0.578	0.445	13.89			
7	1,450	1.021	1.481	0.409	0.405	14.76			
8	1,100	1.027	1.474	0.448	0.451	13.05			

*Creatinin* The creatinin in the urine averages 22.6 mg per kilo body weight, which is normal<sup>1</sup>. It is very constant from day to day, showing how completely and carefully the urine was saved. The variations from day to day were unusually slight, they are ordinarily

<sup>1</sup> In a case of pseudohypertrophic muscular dystrophy Springer (The Excretion of Creatinin in a Case of Pseudohypertrophic Muscular Dystrophy, Biochem. Ztschr. 1907, ii, 205) found low creatinin excretion.

greater than found in this case. But we should like to point out—as a result of abundant experience—that when the twenty-four-hour quantities of urine are completely collected and the diet is constant and free from creatinin-producing substances, the excretion of creatinin is very constant, the variations being not more than 0.02 or 0.03 gm per day from day to day.

**Creatin.** Creatin is present in large quantities. This is abnormal. By this method of creatin determination, which, we are convinced, is more reliable than the newer methods that appear to show traces of creatin even in normal urine, normal urine shows no creatin whatever.

**Ammonia.** The ammonia is normal in amount. This is significant. Other conditions in which creatin has been found present are associated with high ammonia excretion. In this case the low ammonia and absence of acetone and diacetic acid shows that we are dealing with a case of creatin-urea not accompanied by acidosis.

The uric acid, total nitrogen, calcium, and magnesium show no marked abnormalities, though the ratio of calcium to magnesium is rather high.

**Blood Examinations.**—Blood examination showed the results set forth in Table 7.

TABLE 7—BLOOD EXAMINATIONS

	Mg. Per 100 Gm.
Creatinin	1.43
Creatin	3.86
Nonprotein nitrogen	28.9
Uric acid	2.30
Glucose	0.073 per cent
Cholesterol	0.050 to 0.144 per cent

**Glucose.** The glucose in the blood is low. Methods for the accurate quantitative determination of glucose in small amounts of blood have been available within only a very short time. Examination by these methods shows that the normal amount of glucose in the blood varies within very narrow limits and Allen<sup>2</sup> has pointed out that approximately the normal percentage is stubbornly maintained throughout prolonged starvation, almost up to death. By the method we used the variations are from 0.09 to 0.11 per cent according to Lewis and Benedict,<sup>3</sup> from 0.09 to 0.12 per cent according to Myers

2 Allen. Glycosuria and Diabetes, 1913.

3 Lewis and Benedict. Jour. Biol. Chem., 1915, xx, 61.

and Fine<sup>4</sup> Our figures show an average of 0.073 per cent (0.0731, 0.0717, and 0.0747 per cent in three determinations)

**Cholesterin** The cholesterin is very low Of twenty-five determinations of cholesterin which we made in various other diseases all but four showed between 0.19 and 0.26 per cent The four exceptions showed 0.17, 0.17, 0.14, and 0.15 per cent, respectively

The nonprotein nitrogen, uric acid, creatinin, and creatin content of the blood show no abnormalities

#### DISCUSSION

The striking abnormalities were, then, a low glucose and cholesterin content of the blood, and the presence of creatin in the urine

The *creatin* in the urine suggests some abnormality of the glucose metabolism It is found in the urine in conditions like diabetes and starvation when sugar is not being properly oxidized, and in such cases is usually associated with acidosis In the present instance the normal ammonia excretion and absence of acetone and diacetic acid from the urine show that we are dealing with creatinuria without acidosis

The low *cholesterin* content of the blood has no definite significance in the present state of our knowledge of the physiology of this substance The most that can be said is that it makes us think of the possibility of involvement of the adrenals, a possibility that is still further indicated by the hypoglycemia

The association of muscular weakness with *hypoglycemia* is striking, for we know that the muscle gets its power through oxidation of sugar, and a low sugar content of the blood might be looked on as sufficient cause for muscular weakness Many investigators have demonstrated the power of sugar to make exhausted muscles capable of more work, the subject, with literature, is discussed by Furth and Schwarz<sup>5</sup> A direct relationship between muscular weakness and hypoglycemia has been noted by different investigators Weiland,<sup>6</sup> using a Gartner ergostat, had several of his colleagues do severe muscular work, almost to the point of exhaustion, and determined the glucose content of the blood before and after the work In every case there was a decrease in the glucose content of the blood, the average decrease being 27 per cent In three cases of Addison's disease — a condition

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4 Myers and Fine Chemical Composition of the Blood in Health and Disease, New York, 1915 The results by older methods are less to be relied on

5 Furth and Schwarz Ueber die Steigerung der Leistungsfähigkeit des Warmblutermuskels durch gennungsbefördernde Muskelgifte, Pflüger's Arch f d ges Physiol, 1909 cxxx, 525

6 Weiland Ueber den Einfluss ermüdender Muskelarbeit auf den Blutzuckergehalt, Arch f exper Path u Pharmacol, 1907-08, xcm, 223



characterized by intense muscular weakness—quantitative determinations of the glucose content of the blood by Porges<sup>7</sup> showed 0.052 per cent, 0.033 per cent, and 0.067 per cent—all very low results. Porges followed this point further in experiments on animals. He removed the adrenals from several dogs and compared the glucose content before and a few hours after the operation. His figures are as shown in Table 8. In every case there was a decrease in the glucose content of

TABLE 8—GLUCOSE CONTENT BEFORE AND AFTER REMOVAL OF ADRENALS

	Per Cent Before	Per Cent After
Dog 1	0.258 0.103	0.0058 0.0057
Dog 2	0.120	0.033
Dog 3	0.034	0.066
Dog 4	0.092	0.044

the blood. Mayer<sup>8</sup> had previously reported a fall in the blood sugar content in cats after removal of the adrenals. This association of fall in blood sugar content with muscular asthenia and decrease in adrenalin is quite in harmony with the fact previously observed by Battelli and Boatti<sup>9</sup> and by Schur and Wiesel<sup>10</sup> that the epinephrin content of the blood of dogs decreases when these animals are made to undergo exhausting work on a treadmill. An association between muscular asthenia and hypoglycemia has been noted in a case of dyspituitarism and in atrophied babies. In Cushing's<sup>11</sup> book on the hypophysis there is a case history of a man suffering from dyspituitarism, showing marked muscular asthenia and low blood sugar (0.039 and 0.053 per cent in two determinations). Frank<sup>12</sup> observed in three atrophied babies, respectively, 0.046 per cent, 0.040 per cent, and 0.050 per cent blood sugar (0.10 to 0.11 per cent is the average figure for normal babies).

Muscular asthenia alone, secondary to some other condition, is not necessarily accompanied by hypoglycemia. Through the kindness of

7 Porges. Ueber Hypoglykämie bei Morbus Addison sowie bei neben-nierenlosen Hunden, *Ztschr. f. klin. Med.*, 1909-10, lxi, 341.

8 Mayer. Ablation des surrenales et diabète pancréatique, *Compt. rend. Soc. de biol.*, 1908, lxi, 219.

9 Battelli and Boatti. Influence de la fatigue sur la quantité d'adrénaline existant dans les capsules surrenales, *Compt. rend. Soc. de biol.*, 1902, liv, 1203.

10 Schur and Wiesel. Beiträge zur Physiologie und Pathologie des chromaffinen Gewebes, *Wien. klin. Wchnschr.*, 1907, xx (2), 1202.

11 Cushing. The Pituitary Body and Its Disorders. Phila., 1910, p. 130.

12 Frank. Ueber einige Grundtatsachen aus der Physiologie des Blutzucker nebst methodischer Vorbemerkungen, *Ztschr. f. physiol. Chem.*, 1910-11, lxx, 129.

Dr Goldthwait we had an opportunity to examine the blood in two very rapidly progressing cases of chronic arthritis of the infectious type, one of them of less than twelve months' duration, the other of less than six months' duration. In both cases there was a very marked wasting of the muscles. Examination showed 0.119 per cent and 0.120 per cent blood sugar, respectively, in the two cases. The significant feature in these cases was not muscular weakness alone, but rather muscular wasting.

As to the cause of the low sugar content of the blood, two possibilities may be imagined.

1 Hypoglycemia can be brought about by a lowered threshold value for excretion of glucose through the kidneys—renal diabetes. Thus the sugar content of the blood can be lowered by the administration of phloridzin, a drug which increases the permeability of the kidney for glucose and causes glucosuria. With the patient we had under observation the fact that glucose was absent from the urine excludes this as a possible cause of the hypoglycemia.

2 Glucose is constantly passing from the blood into the muscles to undergo oxidation, this loss is made up by the introduction of glucose into the blood from the glycogen store in the liver, and hypoglycemia can be brought about as the result of loss of balance between the rate at which glucose is introduced into the blood and the rate at which it disappears from the blood into the muscles. This regulation of the rate of formation of glucose from glycogen is under the control of the adrenals, the pituitary body and the thyroid gland,<sup>13</sup> administration of these substances or stimulation which increases the amount of adrenal principle in the blood leads to hyperglycemia.<sup>13</sup> That the cause of hypoglycemia in Addison's disease and after removal of the adrenals is associated with a decreased formation of glucose from glycogen is evident from the experiments of Porges,<sup>14</sup> who showed that after removal of the adrenals from dogs the liver becomes practically free from glycogen. Porges<sup>15</sup> followed the subject still further and noted that adrenal principle increases not only the rate of formation of glucose from glycogen, but also the rate of formation of glycogen from glucose, so that when the adrenals are diseased the liver loses its power to store glycogen. Frank and Isaac,<sup>16</sup> furthermore, have shown that the hypoglycemia resulting from phosphorus poisoning results from a loss of power of the liver to store glycogen.

13 The literature on this subject is voluminous.

14 Porges. Ueber Hypoglykämie bei Morbus Addison sowie bei neodenierelosen Hunden. *Ztschr f klin Med* 1909-10 LVII, 341.

15 Porges. Zur Pathologie des Morbus Addison. II. Ueber Glycogenschwund nach doppelseitiger Nierenentstirpation bei Hunden, *Ztschr f klin Med* 1910 LXX 243.

16 Frank and Isaac. Ueber das Wesen des gestörten Stoffwechsels bei der Phosphorvergiftung. *Arch f exper Path u Pharmacol* 1910 LXV, 272.

The possibility that the low sugar content of the blood in our case might be due to inability to store glycogen as effectively as normally, led us to determine the glucose content of the blood after a short period of starvation. Normally, as fast as the glucose of the blood is oxidized, a continuous new supply resulting from glycogenolysis maintains the glucose of the blood at its normal level, starvation and ingestion of food has but little effect on the glucose content of the blood. Any interference with glycogen storage might become apparent by a fall of the glucose content of the blood after a short period of starvation. It was not our purpose really to starve the patient, but merely, by omitting a meal, to exclude the effect of food on the glucose content of the blood, the patient was asked merely to omit his breakfast on one day. He went without food from 6 p. m. one evening until noon the next day, when blood was again taken for examination. The glucose content was 0.064 per cent (triplicate determinations showed 0.0651, 0.0628 and 0.0637 per cent, respectively) at this time — decidedly lower than when previously taken. The decrease is at least suggestive, though not of course to be taken as definite indication of any disturbance in glycogenolysis.

Another fact of interest to be mentioned here is the relationship between loss of power to store glycogen and fatty transformation. In one of his experiments on dogs Porges<sup>15</sup> noted that during the operation of removing the adrenals the liver was normal, at necropsy, shortly afterward, it was observed that the liver had undergone fatty transformation, in other words, fat was stored instead of glycogen. A similar observation is recorded by Frank and Isaac,<sup>16</sup> these investigators noted that the loss of power of the liver to store glycogen which results from phosphorus poisoning was accompanied by a storage of fat instead. The fact noted by Cushing<sup>11</sup> that fatty transformation of the liver cells accompanies states of hypopituitarism — another condition associated with muscular weakness and hypoglycemia — may be mentioned in this connection. In view of these facts showing a relationship between hypoglycemia, fat storage and loss of power to store glycogen, the significance of the deposition of fat in the muscle cells in cases of pseudohypertrophic muscular dystrophy becomes apparent, the fat storage may well be due to an inability of the muscle to exercise its normal function of storing glycogen, fat instead being stored.

#### TREATMENT

In view of the facts connecting hypoglycemia, muscular asthenia and diminished activity of the adrenals and hypophysis, Dr. Spear suggested the use of epinephrin and pituitary extract for treatment. A detailed report of the treatment and its results will be made elsewhere. The point to be brought out here is the relationship between improvement in the physical condition and the increase in blood sugar.

Improvement in health, strength and weight was prompt and marked, and, with the improvement, the sugar content of the blood rose first to 0.080 per cent then to 0.099 per cent, the latter a normal amount. An increase in the cholesterol content of the blood accompanied the increase in sugar content, with 0.080 per cent sugar the cholesterol content was 0.177 per cent, with 0.099 per cent sugar the cholesterol content was 0.211 per cent, the latter a normal amount.

As a preliminary to leaving our care entirely and returning to his home, the patient was allowed to leave the hospital and do much as he pleased in the city. At the end of a week his condition showed no change, the blood sugar showed a slight drop to 0.087 per cent, a figure which is only slightly below the normal average.<sup>17</sup>

It may be wise here to warn for the present against any attempts to treat such conditions by intravenous administration of glucose, a form of treatment that might naturally suggest itself. Underhill<sup>18</sup> tried this form of treatment on three dogs which showed hypoglycemia and muscular asthenia as a result of hydrazin poisoning, the animals all died within a few hours.

#### SUMMARY

In a case of progressive muscular dystrophy, the creatinin excretion was normal, large amounts of creatin were found in the urine, the ammonia excretion was low, there was no evidence of acidosis, the amount of sugar in the blood was low, the cholesterol content of the blood was low. A relationship between sugar content of the blood and ingestion of food suggested the possibility of a decreased power to store glycogen. Treatment which increased the glucose and cholesterol content in the blood led to improvement in the clinical condition.

We intend to follow this subject further. But since this disease is not common, our present results are published in order to call attention to the desirability of determining blood sugar in other cases of a similar nature. If confirmed in other cases, the association of hypoglycemia and muscular asthenia in this disease is, of course, of great significance in the physiology of carbohydrate metabolism.

Robert Breck Brigham Hospital

<sup>17</sup> Two months after leaving us we received a letter from the patient who is in a distant part of the country, stating that he had continued taking epinephrin and pituitary extract, that he had gained much in weight and strength and that his muscles were larger and firmer.

<sup>18</sup> Underhill. *Studies in Carbohydrate Metabolism. I. The Influence of Hydrazin upon the Organism with Special Reference to the Blood Sugar Content*, Jour Biol Chem. 1911-12, 2, 159.

# A CLINICAL STUDY OF DELAYED GASTRIC EMPTYING

BASED ON 185 CONSECUTIVE CASES OCCURRING IN AN UNSELECTED  
SERIES OF 1,600 PATIENTS WITH DIGESTIVE SYMPTOMS

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## 1 OBJECT OF STUDY, MATERIAL, METHOD

The object of our study was to determine the general incidence, and, as far as possible, the actual causes of delayed emptying of the stomach as met with in general practice. For this purpose we reviewed the records of 1,600 patients complaining of disturbances of digestion. Not all of these were suffering from actual lesions of the digestive tract. Many patients, as might be expected, had their primary source of trouble in other systems, such as the pulmonary, cardiorenal, or nervous.

The diagnosis of delayed emptying was made from the evidence furnished by tube or Roentgen-ray examinations, or both. For the tube test, the patients were asked to eat an "ordinary dinner" of soup, potato, meat, bread and butter, and a simple dessert such as rice pudding. As substitutes for such a meal, where necessary, we employed a "breakfast" of eggs, toast and cereal, or a "light lunch" (omitting meat, otherwise the same as the dinner). A stomach residue obtained seven hours after the dinner,<sup>1</sup> six hours after the lunch, or five hours after the breakfast, was regarded as pathological. The actual choice of food was always left to the patient, our purpose being to have him select a meal that he would ordinarily (namely, when well) dispose of without symptoms. Moreover, the patient was simply instructed to

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<sup>\*</sup> Submitted for publication Jan 12, 1916

<sup>1</sup> The reason for taking seven hours as the outer limit of the normal is, first, because it is known that the normal stomach digests food ordinarily considered difficult in less than six hours, and secondly, because our meals are so arranged that rarely over six hours elapses between them. The normal stomach is no doubt capable of considerable latitude in the quantity of food it can hold. The weak or sick stomach, on the other hand, objects to undertaking the digestion of the new meal before it has disposed of the old. The symptoms may be due either to the increased load or to the disturbed chemistry, the gastric secretions at the end of digestion being different from what they are at the beginning.

take the meal in question, and to present himself after the appropriate interval, not having partaken of food or drink in the meantime. The exact nature of the examination was usually not disclosed. Finally, as the tube had generally been passed at least twice before (aspiration of fasting stomach and of Ewald test breakfast), it is believed that the psychic factor was reduced to a minimum.

The Roentgen-ray diagnosis of the condition was made from a visible residue six hours after the ingestion of the Rieder meal. In our earlier cases we used 50 gm of bismuth subcarbonate in 300 gm of cereal. Subsequently we employed 100 gm of barium sulphate in cereal or in 500 cc of buttermilk. In accordance with other workers we found the emptying time of all of these combinations to be practically the same under similar circumstances.

We believe that the Roentgen-ray investigation of gastric emptying should always be supplemented by the use of the stomach tube<sup>2</sup> after the administration of "natural" motor meals as suggested above. Since our adoption of this practice we have discovered the existence of delayed emptying in a surprisingly large number of individuals who got rid of their opaque meal within the normal time limits. These cases, which numbered thirty in our series, or about 21 per cent of the total, have been indicated by a star for more ready differentiation in the accompanying large table. To be sure they represent the milder forms of delay due generally to pyloric spasm (occasionally to atony of the stomach), and not to actual obstruction. Although of little interest to the surgeon they are of great importance to the patient, and their existence should be borne in mind by the student of this condition.

## II THE INCIDENCE OF DELAYED GASTRIC EMPTYING

*General Incidence*—In our total of 1,600 cases presenting gastric symptoms, delayed emptying of the stomach occurred 185 times, a general incidence of 11.5 per cent.<sup>3</sup>

*Sex Incidence*—The sex and age incidence were computed from a total of 898 gastro-intestinal cases examined roentgenologically. Of the 483 men in this group, 78, or 16.1 per cent, showed delay. Of the

2 Bassler (Diseases of the Stomach and Upper Alimentary Tract. Phila., F. A. Davis Co., 1913, p. 213) and Cole (Relation of Lesions of the Small Intestine to Disorders of the Stomach and Cap as Observed Roentgenologically, Am Jour Med Sc., 1914, cxlviii, 92) have recommended the addition of an opaque substance to an "ordinary" meal, and employ only the Roentgen ray in this diagnosis.

3 For the purpose of more careful study and for the compilation of some of our data, we selected from the total 185 cases, 141 which were studied roentgenographically. These will be referred to hereafter as the "Roentgen-ray series." Protocols of these cases are given in tabular form at the end of the article (Table 2).

415 women, 63, or 15.1 per cent, were slow in emptying their stomachs. This slightly greater frequency in man is perhaps due to the higher incidence of duodenal ulcer.

*Age Incidence*—Of 464 patients under 40 years, 62, or 13.3 per cent, showed delay, whereas of 252 men 40 or over, 48, or 19 per cent incidence was 79, or 18.2 per cent. The distinctly greater frequency in later years is explained possibly by the practical limitation of cancer to that period of life. In addition, obstructing ulcers are more frequent as age advances.

*Age and Sex*—The distribution of the delay cases in regard to both age and sex was as follows. Of 231 men under 40, 30, or 12.9 per cent, showed delay, whereas of 252 men 40 or over, 48, or 19 per cent, came under this head. Of 233 women under 40, 32, or 13.7 per cent, showed delay, whereas of 182 women 40 years or over, 31, or 17.6 per cent, were slow in emptying their stomachs. For some reason delayed gastric emptying seems to be more common in women than in men under 40 years, a finding not in accord with the generally higher incidence in the male sex.

### III THE CHIEF FACTORS INFLUENCING GASTRIC EMPTYING

The chief factors influencing gastric emptying may be enumerated categorically as follows:

- |                     |                            |
|---------------------|----------------------------|
| 1 Shape of stomach  | 4 Acidity of gastric juice |
| 2 Character of meal | 5 Nervous factors          |
| 3 Tone of stomach   | 6 Mechanical obstruction   |

*Shape of Stomach*—As a general rule it is safe to say that the nearer the pylorus is to the lower pole, the sooner will the stomach get rid of its contents. Thus, a cow-horn stomach (pylorus at lowest point) will empty itself of the Rieder meal in two to three hours. As the fish-hook type is approached, the time lengthens to four or five hours. On the other hand, that a high placed pylorus (so-called water-trap stomach) will in itself cause pathological increase in the emptying time is, to say the least, not easy to prove. Theoretically, of course, it may be possible, and it has recently been claimed (Satterlee and LeWald<sup>4</sup>) that the water-trap stomach may be a rather prominent factor in producing delayed gastric emptying. We have carefully studied and measured over 350 plates with this point in view, but have been unable fully to confirm this finding. In only one of our 185 cases was a water-trap stomach the only pathological condition present, and

<sup>4</sup> Satterlee, G. R., and LeWald, L. T. One Hundred Cases of Water-Trap Stomach, Jour. Am. Med. Assn., 1913, lxi, 1340.

we are forced to conclude, therefore, that in most, if not all, cases of "hypomotility" associated with the peculiarity in question, the cause of the delay must be sought for in some other factor than in the abnormal shape of the organ .

*Character of the Meal*—The amount, chemical nature, and physical form of the food selected, each play an important rôle in determining the emptying time. Thus, an opaque meal of the ordinary bulk leaves the stomach sooner than a full dinner, carbohydrates leave sooner than proteins or fats, fluids sooner than solids.

*Tone of Stomach*—Normally the stomach "grasps" its contents firmly, and is seen roentgenographically to be filled to the cardia. This so-called peristaltic function of Stiller is impaired in muscular weakness (atony or myasthenia gastrica). The Roentgen-ray appearance in this condition is characteristic. The stomach is generally, though of course not necessarily, ptosed, the *Magenblase* long and pyriform, the pars media is the narrowest portion of the organ, the walls often being in contact. Both the transverse and vertical diameters through the incisura angularis are excessive. In contrast to the normal state, the stomach looks and fills like a sack. The peristalsis is generally, though not necessarily, diminished, the essential feature, however, is the inability of the organ to accommodate itself to the size of the load. Atony of the circular fibers, in which the stomach enlarges laterally instead of longitudinally (Todd<sup>5</sup>), is probably of less clinical importance than the type just described.

Atony is rightly regarded as a prominent cause for the inability of the stomach to propel its contents forward. Of 240 cases of atonic stomach, 73, or over 30 per cent, failed to expel the Rieder meal in the proper interval. Conversely, over one-half (54.6 per cent) of the Roentgen-rayed cases of delayed emptying showed atony. In many instances (see Section IV) this was the most prominent, and very often the only, organic finding.

*Acidity of Gastric Juice*—Although this factor might theoretically be grouped under the head of nervous influences, it seems better for practical purposes to consider it in a section by itself. Generally speaking, the less the acidity, the more rapid the emptying, and the higher the acidity, the slower the emptying. Thus, in "anacidity" we speak of a loss of the pyloric reflex, and in "hyperacidity," of a spasm of the pylorus.

In order to obtain a more precise idea of these relationships we calculated the incidence of delayed emptying in our "anacidity" cases

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<sup>5</sup> Todd, T. W. The Clinical Anatomy of the Gastro-Intestinal Tract. New York, Longmans Green & Co., 1915, p. 89.



on the one hand, and in our "hyperacidity" cases on the other, and compared these findings with the general incidence of delayed gastric emptying

Of 154 "anacidities" 14, or 9 per cent, showed delay, of 748 "hyperacidities" 78, or 10.4 per cent, showed delay. However, the interfering influence of obstruction, at least, should be considered. Making a rough correction for this factor by subtracting from each group those cases showing the presence of food in the fasting stomach, the figures become 4.5 per cent for the former, and 9.4 per cent for the latter. Thus the incidence of delayed gastric emptying is twice as great in nonobstructive "hyperacidity" cases as it is in nonobstructed stomachs with "anacidity."

*Nervous Factors*—The nervous system may influence the emptying of the stomach in two possible ways. The first and most important is by the closure of the pyloric sphincter in response to some irritant. In many, though by no means in all, cases, the expression of this irritant seems to be an "increased acidity" of the gastric juice. Clinically, spasm may arise directly from causes within the stomach, such as ulcer, or "reflexly" from causes without the stomach, as in disease of the gallbladder. Roentgenoscopically, pylorospasm is often associated with hyperperistalsis.

Another type of nervous disturbance connected with retarded propulsion is that which occurs in fatigue, emotional states, or intoxications. This is to be distinguished from the first type in that the cause is general or systemic and the pathological condition is probably one of entire inhibition of gastric activity. Thus, it has been shown that in frightened animals the secretory as well as the motor functions are held in abeyance. This point will be discussed further (Section V).

*Mechanical Obstruction*—Foreign bodies, hair balls, for example, seem seldom to obstruct the lumen of the stomach sufficiently to cause delay in emptying. Within the wall of the stomach the most frequent causes are new growths or cicatrized or indurated ulcers at the pylorus. Edema of the gastric wall as a result of ulcer is a possible cause of delay, though clinically this cannot be distinguished from spasm. The chief extragastric factors are tumors or adhesions usually located in the neighborhood of the pylorus. These may of course act reflexly by interference with the nerve supply.

#### IV THE IMMEDIATE OR ACTUAL CAUSES OF DELAYED GASTRIC EMPTYING

For all practical purposes, there are but three immediate causes of delayed gastric emptying. They are, in the order of their frequency, spasm, obstruction, and atony. Their respective incidence in our Roentgen-ray series was as follows:

	Cases	Per Cent
Spasm	83	or 58.8
Obstruction	30	or 21.2
Atony	24	or 17.0
Undetermined	4	or 2.8

Naturally, two or even all three of these causes may be present at the same time. In computing the foregoing figures only the most prominent cause was used in each instance.

#### V DISEASES PREDISPOSING TO DELAYED GASTRIC EMPTYING

The clinical conditions met with, and perhaps responsible for, the delayed gastric emptying in our entire series of 185 cases, are presented in the accompanying table (Table 1). Unfortunately, we were unable to control these findings in many instances by repeating the tests after the presumptive cause was removed. Although the individual diagnosis may be open to objection, we feel that our conclusions in general are as nearly accurate as work done under the conditions of ordinary practice will permit. It should be mentioned also that the groups into which our cases are divided are not necessarily mutually exclusive. Thus, many of the patients presented more than one of the seventeen conditions or diseases considered in the table. For the sake of simplicity, however, only the most prominent condition was considered in each case in working up the material.

TABLE 1—CLINICAL DIAGNOSIS IN 185 CASES OF DELAYED GASTRIC EMPTYING

Disease	Cases	Per Cent	Disease	Cases	Per Cent
1 Ulcer	75	40.5	10 Chronic appendicitis	2	1.0
2 Diagnosis not clear	25	13.5	11 After gastro-enterostomy	2	1.0
3 Unexplained high acidity	17	9.1	12 Extragastric pressure	2	1.0
4 Autointoxication (including migraine)	14	7.5	13 Carcinoma of colon	1	0.5
5 Carcinoma of stomach	14	7.5	14 Mucous colitis	1	0.5
6 Ptosis with atony	13	7.0	15 "Constipation"	1	0.5
7 Cholelithiasis	7	3.7	16 Nephrolithiasis (?)	1	0.5
8 Adhesions (intestinal)	5	2.7	17 Apprehension neurosis	1	0.5
9 Tuberculosis (systemic, including pulmonary)	4	2.1			

Gastroduodenal ulcers seem to be responsible for about half the cases of delayed emptying. Our incidence of 40.5 per cent represents a conservative estimate, since all doubtful cases were thrown into one of the two following groups. A positive diagnosis of duodenal ulcer was made in thirty-eight cases, or in 50.6 per cent of the series. Obstructing ulcers at the pylorus (food in fasting stomach) occurred

twenty-five times, or in 33.3 per cent of the cases. Thus a reasonably certain diagnosis of the situation of the ulcer was made in 84 per cent of the cases.

Cases of autointoxication with so-called bilious or migraine attacks formed a fairly large group in the series. Although well known to special writers on the subject (an interesting chemical study of a case is reported by Harley and Goodbody<sup>6</sup>), the frequency of the association of this condition with delayed emptying of the stomach is perhaps not fully enough appreciated. The relief obtained by many of these patients from vomiting is a striking illustration of the intimacy of this relationship. Just what this relationship is as regards cause and effect, we are not able to say. All of our cases happened to be examined in the interval between attacks.

The carcinoma cases were of the obstructing type situated at the pylorus. The colloid variety, which can be diagnosed readily, and in most cases only, by the Roentgen ray, is of course associated with gastric "hypermotility."

The group designated "ptosis and atony" is of great interest. It includes those cases of "asthenia universalis" so well described by Stiller.<sup>7</sup> The recognition and correction of both the underlying conditions completely change the outlook for many of these sufferers. One of the women in this category was lactating at the time of the examination. It is interesting to speculate how much this state had to do with the gastric delay. As long ago as 1883, v. Leube<sup>8</sup> pointed out that menstruation was in itself likely to increase the emptying time of the stomach.

In two of the patients operated on for cholelithiasis a large, tense gallbladder was found. It is possible that the delay may have been due to actual pressure as well as to reflex spasm.

The tuberculosis cases were made up as follows. Three were pulmonary, two, strange to say, with achylia, the fourth was a case of bone tuberculosis. A fifth case, with gastric ulcer, had lesions of the kidney and testicle. If the "hypomotility" in these cases is really due to the tuberculosis it may be assumed that the delay is brought about by a severe systemic intoxication. This may therefore be an illustration of the second type of nervous disturbance described in Section III.

Chronic appendicitis was not often met with in our series. We made a positive diagnosis in but two cases (1 per cent), a rather low inci-

6 Harley, V., and Goodbody, F. W. *The Chemical Investigation of Gastric and Intestinal Diseases*. London, E. Arnold, 1906, p. 83.

7 Stiller, B. *Enteroptose im Lichte eines neuen Stigma neurasthenicum*, *Arch. f. Verdauungskr.*, 1896, 11, 285.

8 Von Leube, W. *Beiträge zur Diagnostik der Magenkrankheiten*, *Deutsch. Arch. f. klin. Med.*, 1883, 22, 8.

dence, but apparently in keeping with the findings of Carman and Miller<sup>9</sup>

A further comparison of our findings with those of the Mayo Clinic may be made from the following table

Disease	Incidence in "Hypomotility" Series	
	Carman and Miller	Levy and Kantor
Lesions of the appendix	12	10
Lesions of the gallbladder	50	37
Gastroduodenal ulcer	57.0	50.0 (estimated)
Gastric cancer	36.0	7.5
"Nonsurgical" conditions		36.4

In the two cases of delayed emptying following gastro-enterostomy, the indications for the operation were by no means clear in the first place

The two cases of extragastric obstruction were, respectively, an extensive retroperitoneal sarcoma in a negro, and a very large liver and spleen of undetermined etiology in a boy of 7

Lesions of the intestine are supposed to cause gastric delay reflexly, perhaps through pylorospasm. Our series includes, in addition to appendicitis, cases of adhesions, carcinoma of the colon, mucous colitis<sup>10</sup> and severe constipation. In all, lesions of the intestine were present in over 5 per cent of our cases of delayed gastric emptying.

The association of the phobias (apprehension neurosis) with digestive disturbances is no new observation. Oppenheim<sup>11</sup> mentions an interesting case of astrophobia which presented the symptoms of weakness, nausea, and vomiting. The patient's 8-year-old son was not afraid of storms, but showed the same digestive disturbances as his mother. Both of our patients were afraid of crowds. One of the cases was associated with autointoxication. We have records of seven other cases with digestive symptoms but without delayed gastric emptying. A possible explanation of the "hypomotility" in this condition may lie in the fact that the emotional state in these patients is in reality one of chronic fear, analagous to the acute fear induced in the animals observed by Cannon<sup>12</sup>. Here there was noted complete absence of peristalsis. This seemed to be the case in one of our patients, in the other the peristalsis was hyperactive.

9 Carman, R. D., and Miller, A. The Roentgenologic Determination of Gastric Motility, *THE ARCHIVES INT. MED.*, 1915, xvi, 406

10 Herschell (Indigestion. London, H. J. Glaisher, p. 104) makes much of the association of mucous colitis with gastric myasthenia. The bowel symptoms, which would naturally follow from gastric "hypomotility" from any cause, are the result of the continuous discharge into the intestine of improperly digested material.

11 Oppenheim, H. *Lehrbuch der Nervenkrankheiten*. Berlin, 1913, p. 1521

12 Cannon, W. B. *The Mechanical Factors of Digestion*. New York, Longmans, Green & Co., 1911, p. 217, *Bodily Changes in Pain, Hunger, Fear, and Rage*. New York, D. Appleton & Co., 1915, p. 16

TABLE 2—ONE HUNDRED FORTY-ONE CASES OF DELAYED GASTRIC EMPTYING STUDIED ROENTGENOLOGICALLY  
("ROENTGEN-RAY SERIES")

No	Sex	Age, Years	Residue		Fasting Contents, c.c.	Ptosis, cm	Atony	Acidity	Water Trap	Clinical Diagnosis	Probable Cause of Delay
			Tube	Roentgen Ray							
1	M	35	8½ h D 120	6 h sm	120	9	0	Hyper	—	Duodenal ulcer	Spasm
*2	M	60	6 h D 240	0	30	12.5	+	Hyper	—	Duodenal ulcer	Spasm, atony
3	M	46	4 h B +	6 h +	—	9	++	Hyper	—	Ptosis and atony	Atony, spasm
4	M	23	6 h L +	6 h sm	Normal	10.5	SI	Hyper	+	?	Spasm
*5	M	37	6 h D 180	0	Normal	7.5	+	Normal	0	Duodenal ulcer	Atony
6	M	50	7 h L 370	6 h sm	70	11.5	0	Hyper	0	Ulcer	Spasm
7	M	67	6 h D +	6 h +	180	+	+	Hyper	—	Duodenal ulcer	Spasm
8	F M	27	—	6 h sm	Normal	7	0	Normal	+	Intestinal adhesions	Spasm
*9	F M	45	6 h D 300	0	Normal	+	+	Hyper	—	Ulcer, chronic nephr	Spasm
*10	M	30	6 h D 300	0	Normal	3.5	0	Hyper	—	?	Spasm
11	M	30	6 h B 150	6 h sm	—	+	+	Hyper	—	Ptosis and atony	Atony, spasm
12	M	54	6 h L 500	6 h sm	—	+	+	Hyper	—	Ulcer	Atony, spasm
*13	F M	39	7 h D 10	6 h lge	Normal	+	+	Hyper	0	Ulcer, chronic endocarditis	Spasm
					(Three years later chronic gastritis and acidity)						
*14	M	22	6 h B +	0	—	10.5	+	Hypo	0	Ulcer	Atony
15	F S	17	6 h D ++	6 h lge	Normal	9.5	SI	Normal	—	Ulcer	Obstruction
16	M	43	6 h D 300	6 h lge	30	3.5	SI	Hyper	—	Duodenal ulcer	Spasm
17	M	42	—	6 h lge	Hypers	7.5	SI	Hyper	0	Duodenal ulcer	Spasm, obstr ?
18	M	56	6 h D +	24 h +	—	13	++	Hyper	—	Ulcer	Obstruction
19	F M	61	—	6 h lge	—	8	++	Hypo	—	Carcinoma	Obstruction
*20	F S	27	6 h D mod 6 h D lge	0 h sm	Normal (After gastro-enterostomy)	6.5	0	Hyper	—	?	Spasm
					No obstruction found at operation						
*21	M	42	6 h D 60	0	30	4.5	0	Hyper	0	Duodenal ulcer	Spasm

*23	M	23	6 h D lge	24 h sm	Normal	55	0	Hyper	Obstruction
24	F M	53	6 h L + 6 h L 0	6 h sm (After gastro enterostomy, cured)	500 F	85	0	Hyper	Obstruction
25	M	24	6 h D +	6 h sm	Normal	11	SI	Hyper	Spasm
*26	M	30	6 h B 300	0	—	55	SI	Hyper	Spasm
27	M	41	12 h L 30	6 h lge	60 F	9	SI	Hypo	Obstruction
28	M	64	6 h L 1,000	24 h lge	2,000 F	9	+	—	Obstruction
29	M	49	—	6 h lge	1,000 F	5	0	Hypo	Obstruction
30	M	10	—	6 h sm	Normal	55	0	Hyper	Spasm
*31	F M	15	7 h D 50	6 h sm	Normal (Two years later)	10	0	Hyper	Spasm
32	M	41	—	6 h mod	Normal	0	0	Hyper	Spasm
33	M	28	6 h D sm	6 h sm	30	0	0	Hyper	Spasm
34	M	12	6 h D 1,000	6 h sm	Food	0	0	Hyper	Spasm, vicious circle?
35	F M	59	—	6 h lge	500 F	0	0	—	Obstruction
36	M	38	—	6 h sm	Normal	0	0	Hyper	Spasm
37	F M	60	—	6 h lge	Normal	9	+	Normal	Extra gastric obstruction
*38	M	40	—	0	—	0	0	Hyper	Spasm
39	F M	29	—	6 h mod	Normal	95	SI	Hyper	Spasm
*40	M	59	6 h D +	0	Normal	+	+	Hyper	Atony, spasm
41	F S	24	6 h D 500	6 h sm	30	135	+	Hyper	Obstruction?
*42	M	31	6 h D 300	0	Normal	12	+	Hyper	Atony
*43	F S	23	6 h B lge 8 h D 0	0 (After gastro enterostomy and gastropexy)	Normal	12	+	Hyper	Atony
*44	M	40	5 h B lge	0	Hypers	15	0	Hyper	Spasm
45	F M	50	—	6 h mod	Normal	35	0	Normal	?
46	M	52	—	6 h sm	Normal	45	0	Hyper	Spasm
47	M	59	—	48 h +	500 F	12	+	Hyper	Obstruction

TABLE 2.—ONLY HUNDRED FORTY-ONE CASES OF DELAYED GASTRIC EMPTYING STUDIED ROENTGENOLOGICALLY  
("ROENTGEN-RAY SFRILS")—(Continued)

No	Sex	Age, Years	Residue		Fasting Contents, c c	Ptosis, cm	Atony	Acidity	Water Trap	Clinical Diagnosis	Probable Cause of Delay
			Tube	Roentgen Ray							
48	F M	57	7 h D lge	6 h mod	Normal	11	+	Hypo	—	Ptosis and atony	Atony
*49	F S	28	7 h D lge	0	Normal	55	0	Hyper	0	Migraine	Spasm
50	M	42	—	6 h sm	22	8	SI	Hyper	0	Duodenal ulcer	Spasm
51	F S	26	—	6 h +	Normal	10	+	Hyper	—	Autointoxication	Spasm, atony
*52	M	42	7 h D lge	0	Normal	115	SI	Hypo	+	Duodenal ulcer	Atony, water trap?
53	M	55	—	4 h lge	—	0	0	—	—	Retroperit lymphosarc	Obstruction
			(No Roentgen ray examinations after four hours, practically entire meal left then)								
54	F M	81	—	6½ h sm	Hypers	115	+	Normal	—	Ptosis and atony	Atony
55	F M	33	6 h D mod	6 h sm	Hypers	3	SI	Hypo	—	Autointoxication, migr linc	Spasm, atony?
*56	M	22	6 h D mod	0	—	0	0	Normal	—	?	?
*57	M	37	6 h D mod	0	Normal	105	+	Hyper	+	Duodenal ulcer	Spasm, atony
58	M	65	—	2½ h +	500 F	4	0	Hypo	0	Carcinoma	Obstruction
59	F M	62	—	6 h lge	Normal	13	SI	Hypo	+	Tuberculosis	Atony, water trap?
60	M	13	—	6½ h lge	Food	0	0	Normal	—	Adhesions, intestinal	Spasm
*61	M	32	8 h L mod	0	—	14	+	Hyper	—	Gastric ulcer	Spasm
62	M	38	—	6 h +	Normal	0	0	Normal	0	Duodenal ulcer	Spasm
*63	F M	45	6 h D +	0	Normal	85	+	Hypo	+	Cholelith	Spasm
64	F M	50	—	6 h lge	Normal	6	SI	Normal	0	Autointoxication	Spasm
65	T S	20	—	9 h +	Normal	105	0	Normal	0	Tuberculosis	Spasm
66	M	45	—	6 h lge	—	65	0	—	—	Chronic appendicitis	Spasm
67	M	37	6 h D 300 7 h D 200	7 h + 0	Food	10	+	H3 per	+	Duodenal ulcer	Obstruction
			(After gastro enterostomy moderate improvement)								





TABLE 2—ONE HUNDRED FORTY-ONE CASES OF DELAYED GASTRIC EMPTYING STUDIED ROENTGENOLOGICALLY  
("ROENTGEN-RAY SERIES")—(Continued)

No	Sex	Age, Years	Residue		Fasting Contents, cc	Ptosis, cm	Atony	Acidity	Water Trip	Clinical Diagnosis	Probable Cause of Delay
			Tube	Roentgen Ray							
92	M	7	—	6 h sm	—	3.5	0	—	—	Enlarged liver and spleen	Extra gastric obstruction
93	F M	34	6 h D lge	7 h sm	40	10.5	0	Normal	—	Intestinal adhesions	Spasm
94	F M	31	7 h D 100	6 h lge	—	11	S	Hyper	—	Ptosis and atony	Spasm, atony
95	M	68	—	24 h lge	2,000 F	7.5	++	Hypo	—	Ulcer	Obstruction
*96	M	44	7 h D 170	0	Normal	9	0	Hyper	0	Mucous colitis	Spasm
97	F M	56	6 h L 200	6 h sm	Normal	10.5	+	Normal	0	Ptosis and atony	Atony
98	F M	33	7 h D mod	6 h sm	Normal	6	0	Hypo	—	Constipation	Spasm?
99	M	33	7 h L 100	6 h lge	140	10	0	Hyper	0	Duodenal ulcer	Spasm
100	F S	21	—	6 h mod	54	7.5	0	Hyper	0	?	Spasm
101	F M	48	—	6½ h mod	Normal	16	+	Hyper	0	Chronic appendicitis?	Spasm
102	M	45	—	6 h sm	Normal	5.5	0	Hyper	0	?	Spasm
103	F M	52	6½ h D 200	6 h sm	Normal	3	0	Hypo	0	(Chronic endocarditis, achylia gastrica)	?
104	F M	28	—	6¼ h mod	Normal	10	0	Normal	0	Appr neur	Spasm
105	F M	32	6¾ h D 30	6 h mod	Normal	11.5	0	Normal	0	(Chronic endocarditis)	?
106	M	65	—	19½ h lge	500 F	4	SI	Hypo	—	Ulcer	Obstruction
107	F M	47	7 h D 150	6 h sm	Normal	0	0	Hyper	0	?	Spasm
108	M	34	7 h D 150	6½ h sm	—	0	0	Hyper	0	Duodenal ulcer	Spasm
*109	M	52	7 h D 250	0	15	0	0	Hyper	0	(Arteriosclerosis)	Spasm
110	M	24	8 h L 115	6 h lge	165	7	0	Hyper	—	Ulcer	Spasm
111	F M	37	6 h D 50	6 h sm	40	9.5	+	Achylia	0	Ptosis and atony (lactat- ing) ulcer	Atony
112	M	65	6½ h D 150	9 h +	Normal	3.5	0	Normal	+	Ulcer	Spasm
113	F M	40	6½ h L 650	24 h lge	400 F	9	SI	Hypo	0	Ulcer	Obstruction

114	M	9	—	6 h sm	Normal	0	0	Hypo	0	(Nephritis)	Spasm
115	F S	27	—	6¼ h lgc	—	0	0	—	+	Adhesions	Spasm? trap?
116	F M	35	7 h D 100	8½ h sm	Normal	95	+	Hypo	—	Ptosis and atony	Atony
117	F M	30	7 h L 50	6 h lgc	Normal	13	+	Normal	—	Ptosis and atony	Atony
118	M	50	6 h B 80	6 h lgc	270 F	55	Sl	Hyper	—	Ulcer	Obstr, spasm
119	F M	27	7 h D 40	6 h mod	72	135	+	Normal	0	Ptosis	Atony
120	F M	54	6 h B 100	24 h +	210	11	Sl	Hypo	0	Cholelith	Spasm, obstr
121	F M	23	7 h D 70	9½ h mod	Normal	105	0	Normal	—	Autointoxication	Spasm
122	F M	53	—	24 h lgc	400 F	13	Sl	Hyper	—	Ulcer	Obstruction
123	F S	18	7¼ h D 50	6¼ h mod	40	4	0	Normal	0	?	?
124	M	34	7 h B 1,500	24 h lgc	900 F	105	+	Normal	—	Ulcer	Obstruction
125	M	62	7¼ h D 15	6 h mod	Normal	16	+	Normal	+	Ptosis and atony	Atony
126	F M	55	—	7 h mod	100	14	Sl	Hyper	—	Cholelith	Spasm, obstr
127	M	71	6 h B 300	6 h sm	Normal	3	0	Hyper	—	Ulcer	Spasm, obstr
*128	M	53	5¼ h B 150	0	—	13	0	Hyper	0	Duodenal ulcer	Spasm
129	F M	64	7 h B 80	6 h mod	Normal	18	+	Hypo	—	Ptosis and atony	Atony
130	F S	19	7 h D sl	6 h sm	Normal	75	0	Normal	+	?	Water-trap?
131	F S	24	7¼ h D 150	6¼ h mod	Normal	135	+	Hypo	0	Ptosis and atony	Atony
132	F M	55	—	6¼ h mod	Normal	12	0	Achyia	0	Cholelith	Spasm
133	F S	26	—	6 h sm	Normal	10	0	Hyper	0	Adhesions?	Spasm
134	M	40	5½ h B 80	6 h mod	—	75	0	Hyper	+	Duodenal ulcer	Spasm
135	M	40	7 h D lgc	22 h mod	Tr F	75	+	Normal	—	Ulcer	Obstr, atony
136	F S	23	7 h B 60	6 h sl	Normal	12	0	Hyper	+	Autointoxication, chronic appendicitis?	Spasm
137	F M	60	—	6 h lgc	1,300 F	195	0	—	—	Ulcer	Obstruction
138	M	67	7¼ h L 300	6 h sm	—	0	0	Hypo	0	Cancer of colon?	Spasm
139	F M	61	5½ h B 40	6 h mod	Normal	9	+	Hyper	+	Ulcer	Spasm
140	M	38	7 h D 80	6 h mod	95	9	0	Hyper	+	Ulcer	Spasm
141	M	27	—	6 h sm	Normal	155	0	Normal	0	?	Spasm

## EXPLANATION OF ABBREVIATIONS IN TABLE 2

B=Motor breakfast (e g, 7 h B lge=large residue seven hours after motor breakfast)

D=Motor dinner

F=Food

F M=Female, married

F S=Female, single

h=Hours

L=Motor lunch

M=Male

An asterisk (\*) means tube residue but no Roentgen-ray residue

A dash (—) means absence of data

Wherever possible, exact figures are given. Thus, 500 F means 500 c c contents with food. Otherwise, descriptive terms are used, as slight (sl), moderate (mod), large (lge). A zero means the absence of a condition—in the "X-Ray-residue" column it means no six hour residue—a plus sign the presence of the condition, two plus signs its presence in a marked degree.

In the "Fasting Contents" column an amount under 50 c c is considered normal, over 50 c c is hypersecretion, exact figures being given where available. In the "Acidity" column "hyper" means hyperchlorhydria, hyperacidity, or both. "Hypo" means hypochlorhydria, hypoacidity, or anacidity. The normal limits implied are: Free HCl 20 to 40 degrees, total acidity 40 to 60 degrees.

Our clinical findings may be summarized by saying that 74 per cent of the cases of delayed gastric emptying were due to causes residing within the digestive tract, whereas 25.1 per cent were due to causes outside the tract. The stomach itself was the seat of the trouble in 65.1 per cent of the cases.

## VI CONCLUSIONS

1 A rational test for gastric emptying should be based on the patient's ability to get rid of a meal of ordinary bulk and complexity in the usual period, namely, in about seven hours. The "fasting contents" tube test, and the Roentgen-ray test, as commonly employed, are not sufficiently delicate for many clinical purposes.

2 Approximately one in every eight or nine patients with digestive complaints suffers from delayed gastric emptying.

3 The chief factors to be considered in working out a case of delayed gastric emptying are (a) shape of stomach, (b) character of motor meal, (c) tone of stomach wall, (d) acidity of gastric juice, (e) nervous influences, (f) mechanical obstruction.

4 The immediate causes of delayed gastric emptying and their relative frequency are (a) spasm of pylorus in 58.8 per cent of the cases, (b) obstruction at pylorus in 22.2 per cent, (c) atony of stomach in 17 per cent.

5 The conditions most commonly predisposing to or associated with delayed gastric emptying are (a) ulcer in about 50 per cent of the

cases, (b and c) autointoxication and gastric cancer, each 7.5 per cent, (d) ptosis with atony, 7 per cent, (e) cholelithiasis, 3.7 per cent

6 The causes of delayed gastric emptying are located in the stomach in 75.3 per cent of the cases, elsewhere in the digestive tract in 10.3 per cent, and outside the digestive tract in 13.4 per cent

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## FURTHER STUDIES OF BIOLOGICAL METHODS FOR THE DIAGNOSIS OF TUBERCULOSIS

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It is a well accepted truth among laboratory workers that biological methods of diagnosis are only relatively specific. This limited usefulness of biological tests is true not only for such as the Abderhalden reaction, for instance, which is still in process of development, but equally true when applied to such widespread tests as Widal and Wassermann reactions.

Theoretically, inasmuch as these reactions depend on the specific biological processes taking place under the conditions of the disease, the biological methods of diagnosis should be strictly specific. The ideal method will be the one by which positive results are obtained in 100 per cent of cases presenting symptoms of the disease, at the same time giving uniformly negative results on examination of individuals not affected by the disease.

The accumulated experience of a number of investigators through a period of years has shown, however, that practically every method is subject to limitations in its specificity, as well as in its sensitiveness, even if performed by experts<sup>1</sup>.

It is generally accepted now, for instance, that a negative Wassermann reaction is only of relative value, and many experienced clinicians are inclined to suspect the positive Wassermann test also when not corroborated by the clinical picture of the case, or by previous history. The agglutinins and precipitins are generally accepted to be mainly group reactions, and only if quantitatively considered may they be of diagnostic value.

The difficulties in the diagnosis of tuberculosis by biological methods seem to be especially great. Even when specific in character, some methods are of but little diagnostic significance on account of extreme sensitiveness, as the von Pirquet test, for example.

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\* From the Research Laboratories of the Western Pennsylvania Hospital, Pittsburgh, and the Tuberculosis Clinic of the Department of Health, New York City

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<sup>1</sup> In addition, the complexity of methods opens a wide field of errors in diagnosis, due to faulty technique.

Many attempts have been made to apply to the diagnosis of tuberculosis methods on which the diagnosis of other infectious diseases are based, as, for instance, the agglutinin, the precipitin, the meiotagmin reaction, and lately, the biochemical test of Abderhalden, but the results obtained were of scientific interest only. The difficulties of applying methods which work satisfactorily in the diagnosis of other diseases, to tuberculosis is especially apparent in case of the complement deviation test. Numerous attempts to work out this method in tuberculosis have been made by many investigators, but on account of the peculiar properties of the organism, it has not been possible to get a preparation of antigen which could be used for this test successfully. Professor Besredka,<sup>2</sup> who succeeded in cultivating tubercle bacilli on an entirely new medium, was induced by the fact that on this medium the organism showed some hitherto unknown properties, to try also the antigenic properties of his new cultures for the complement deviation test. Successful results obtained by Besredka and Manoukhine<sup>3</sup> in their preliminary experiments, were fully confirmed in this laboratory.<sup>4</sup> We found that, although not fulfilling all the requirements of an ideal diagnostic test, the complement deviation with Besredka's tuberculin seems to be very useful. In fact, it was positive in 93 per cent of cases of clinical tuberculosis. At the same time the occurrence of the reaction in cases in which tuberculosis could not be detected clinically, was limited to less than 10 per cent out of a total of several hundred.<sup>5</sup> More recently many investigators have confirmed the diagnostic value of the complement deviation test with the tuberculin of Besredka, and in the hands of some of them,<sup>6</sup> the occurrence of the reaction among patients presenting clinical symptoms of the disease is even as high as 95 per cent. In controlling the test by a Wassermann reaction,<sup>7</sup> we have been surprised from the beginning, to find that a comparatively large number of serums, reacting with the tuberculin of Besredka, showed a positive Wassermann test<sup>8</sup> also.

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2 Besredka *Compt rend Acad d sc*, 1914, clvi, 1633

3 Besredka and Manoukhine *Compt rend Soc de biol*, 1914, lxxvi, 180

4 Bronfenbrenner *Proc Soc Exper Biol and Med*, 1914, xi, 92

5 Bronfenbrenner *Ztschr f Immunitatsf, Orig*, 1914, xxiii, 221

6 Inman *Lancet*, London, March, 1914, p 4734, also *Compt rend Soc de biol*, 1914, p 251. Renaut *Compt rend Soc de biol*, 1914, p 865. Debains et Jupille *Compt rend Soc de biol*, 1914, p 199

7 As the tuberculin contains lipins derived from the medium on which the tubercle bacilli are grown, and thus there was a possibility that certain nontuberculous serums having lipotropic properties, as for instance syphilitic serums, might fix the complement with this antigen, this control was deemed necessary

8 Bronfenbrenner *Proc Soc Exper Biol and Med*, February, 1914, p 92

## INTERFERENCE OF LIPINS WITH ANTIGENIC PROPERTIES OF TUBERCULIN

The first explanation of the coincidence of the positive tuberculosis and Wassermann reactions naturally was that the serum which had a high lipotropic coefficient fixed with tuberculous antigen also on account of the lipins it contains

We<sup>9</sup> studied this possibility in a number of cases and found that whenever the complement deviation with Besredka antigen is present in serums with high lipotropic properties, it depends on the presence of a separate tuberculous antibody possessing its own index, different from the lipotropic index of the same serum. We found, moreover, that the lipins which can be extracted from the tuberculin with ether, chloroform, benzoin or petroleum ether, are not sufficient, in the quantity in which they are present in the tuberculin, to cause a fixation of the complement in the presence of lipotropic serums.

In order to avoid even the possibility of such nonspecific reaction, however, we repeated our earlier suggestion to deliponize the tuberculin.<sup>8</sup>

In a large series of experiments performed in this laboratory by Dr J. Rockman, in which the tuberculin of Besredka was deprived of lipins by means of extraction by ether, it was found that the antigenic properties of the tuberculin were not injured thereby.<sup>10</sup> In later experiments instead of extracting the lipins from the antigen of Besredka, we succeeded in isolating the active principle of the tuberculin by means of precipitation with ten volumes of absolute alcohol. Another efficient method was the precipitation of protein from the tuberculin by adding two drops of glacial acetic acid to 10 cc of Besredka tuberculin, which produced a heavy precipitate. The precipitate, when centrifuged, suspended in 10 cc of physiological salt solution and neutralized to phenolphthalein, proved to be an excellent antigen, practically free from any lipin except the small amount adherent to the precipitate.<sup>11</sup>

Although, as we previously said, in our early work with the first sample of the tuberculin of Besredka our conclusions were that the amount of lipins present was not sufficient to cause nonspecific fixation of complement in the presence of highly lipotropic serums, the importance of freeing the tuberculin of all its lipins became especially evident in later experiments. We noticed that different samples of tuberculin received by us at different times from Professor Besredka's laboratory, differed in their antigenic properties. The most striking

9 Bronfenbrenner. *THE ARCHIVES INT. MED.*, 1914, xiv, 786

10 Similar findings were reported since, also by Renaut. *Compt. rend. Soc. de biol.* 1914, lxxvi, 865

11 Bronfenbrenner and Rockman. *Biochem. Bull.*, 1914, iii, 381

feature of the differences noticed in a large series of cases was the apparent power of one sample especially (No 4) to fix complement in presence of nontuberculous lipotropic serums. The study of this phenomenon revealed that the cause for such irregularity in the behavior of the sample of Tuberculin 4 was due to the comparatively high lipin content.

The actual quantitative estimate of lipins in different samples of the tuberculin of Besredka was made as follows: 10 cc of each of the different samples were precipitated with 2 drops of glacial acetic acid, thus removing the coagulable protein from the tuberculin. The coagula were repeatedly extracted with alcohol-ether mixture and the extracts thus obtained were evaporated to dryness. The resulting residues of lipins were taken up with 0.2 cc of methyl alcohol and each sample was diluted to the original volume of tuberculin (10 cc) by the addition of the respective supernatant fluid resulting from the precipitation by acetic acid of coagulable protein from each sample of tuberculin.

These emulsions of lipins were then used as if they were syphilitic antigen in parallel series with a preparation of lipins originating from beef heart, which we are using for the routine diagnosis of syphilis<sup>12</sup>. All the emulsions were tested in varying quantities against a constant amount of complement, amboceptor and known syphilitic serum.

TABLE 1—COMPARATIVE DATA ON LIPIN FRACTIONS FROM BESREDKA TUBERCULIN AS SYPHILITIC ANTIGENS

	0.1 cc	0.07 cc	0.05 cc	0.03 cc	0.02 cc	0.01 cc	0.007 cc	0.005 cc	0.003 cc
Syphilitic antigen	+	+	+	+	+	+	±	±	—
Lipins from Tuberculin IV	+	+	±						
Lipins from Tuberculin III	—	—	—						
Lipins from Tuberculin II	—	—	—						

It was found that, when concentrated many times, the emulsions of lipins from Tuberculin II, and especially III, were also able to fix the complement with syphilitic serums, but, *in the amount in which they were present in the tuberculin*, they were not able to cause the non-specific fixation (Table 1). The sample of Tuberculin IV, however, as it appears from Table 1, contained originally an amount of lipins which in the dose of 0.05 cc of the original concentration in the tuberculin already caused fixation of complement with leucic serums. If such tuberculin is used in its original form in the complement deviation test with serums possessing a high lipotropic index, it is evident that a certain number of nonspecific fixations may occur, as can be seen from Table 2.

12 Noguchi and Bronfenbrenner Jour Exper Med, 1911, xiii, 43



TABLE 2—COMPARATIVE FREQUENCY OF FIXATION OCCURRING WITH DIFFERENT SAMPLES OF TUBERCULIN (NONPURIFIED) \*

Twenty Five Cases of Each Group		Tuber- culin II	Tuber- culin III	Tuber- culin IV	Pure Lipoid (Wasser- mann)
No Diagnosis of syphilis	Tuberculosis suspected	24	22	6	0
	Tuberculosis not suspected	1	1	0	0
Diagnosis of syphilis	Tuberculosis suspected	23	22	14	25
	Tuberculosis not suspected	4	5	11	25

\* This table was composed by selecting from the records of all cases examined twenty five for each of the four groups, according to clinical diagnosis with the corresponding serological findings in each case

As Table 2 shows, the sample of Tuberculin IV gives a very high number of fixations in cases of serums with high lipotropic power, irrespective of tuberculous infection. Whereas with the Tuberculins II and III, the occurrence of positive reactions was equal to 16 to 20 per cent in cases in which the Wassermann test was also positive, but tuberculosis not suspected prior to the serological examination,<sup>13</sup> the Tuberculin IV gave 44 per cent of positive reactions in the same cases.

The higher occurrence of fixations with the Sample IV could be attributed to two causes—either this sample was more efficient in detecting tuberculous antibody in the serum, or, on account of its high content of lipin the sample of Antigen IV caused a certain number of fixations of purely lipotropic character and not specific as far as diagnosis of tuberculosis is concerned.

Comparing the frequency of occurrence of the fixation with different tuberculins in the cases of serums with positive and negative Wassermann reactions, respectively, we notice that Tuberculin IV is less efficient in fixing the complement with nonsyphilitic serums than with serums giving a positive Wassermann. We see that in cases diagnosed as tuberculosis with positive as well as with negative Wassermann, its efficiency is much lower than that of Tuberculins II and III. These findings speak definitely against the possibility of the higher specific efficiency of Tuberculin IV being the reason for the greater number of fixations referred to above. It is evident, therefore, that the high percentage of fixations obtained with this sample of tuberculin in cases with positive Wassermann, is due to a certain number of lipotropic reactions.

Although in a number of cases of syphilis we have been able to demonstrate the presence of the two independent antibodies,<sup>9</sup> whenever both the Wassermann and tuberculosis fixation tests were positive, *it is evident that such may not be the case if the antigen used contains an*

<sup>13</sup> This is about the same percentage as we observed in prior series

*excess of lipins* It is therefore imperative to free such a sample of tuberculin of its lipins before using it for the complement deviation work. As a method of doing it, we have found<sup>14</sup> the precipitation with acetic acid to be the simplest.

COMPARATIVE ANTIGENIC VALUE OF DIFFERENT SAMPLES OF TUBERCULIN OF BESREDKA

As Table 2 shows, in the twenty-five cases of tuberculosis in which the Wassermann reaction was negative, and there was no chance of complication due to the lipotropic properties of the serums, the occurrence of positive reactions with Tuberculins II, III and IV was 24, 22 and 6, or 96, 88 and 24 per cent, respectively.

TABLE 3—DETERMINATION OF ANTIGENIC UNIT OF THE PROTEIN FRACTION OF DIFFERENT SAMPLES OF TUBERCULIN OF BESREDKA \*

		Amount of Tuberculin Used (in Cubic Centimeters)												
		0.3	0.2	0.15	0.1	0.07	0.05	0.03	0.02	0.015	0.01	0.007	0.005	0.003
Pulmonary tuberculosis A	Tuberculin II	+	+	+	+	+	+	+	+	+	+	+	±	±
	Tuberculin III	+	+	+	+	+	+	+	+	+	±	—		
	Tuberculin IV	+	+	+	+	+	+	+	±	—				
Pulmonary tuberculosis B	Tuberculin II	+	+	+	+	+	+	+	+	+	±	—		
	Tuberculin III	+	+	+	+	+	+	+	±	—				
	Tuberculin IV	+	+	+	+	+	+	±	—					
No tuberculosis C	Tuberculin II	+	+	±	—									
	Tuberculin III	+	+	±	—									
	Tuberculin IV	±	—	—										

\* The two serums selected for Table 3 were derived, respectively, from cases of first and third stages of pulmonary tuberculosis. We purposely selected these two cases out of the number of serums used for titration of antigens in order to show that the smallest amount of a given antigen sufficient to cause the fixation of complement in presence of one specific serum may not be sufficient when another serum is used. The reason for this difference is the inequality in the amount of antibody in different specific serums. It is therefore imperative always to use in a routine test not the smallest amount of antigen which was found to be sufficient to fix the complement in presence of a certain serum (unit of antigen), but several times that amount, so as to be sure to obtain fixations also in cases in which the amount of specific antibody is smaller. In the cases above, the respective units of Antigens II, III and IV were 0.007 cc, 0.015 cc, and 0.03 cc in case of the serum of a primary stage, and 0.015 cc, 0.03 cc and 0.05 cc in the case of tertiary stage, which indicates that the amount of antibody present in the first case is greater than in the second.

Remembering that the percentage of occurrence of fixation in similar cases reported by us before with Tuberculin I was equal to 93.84, it is evident that in respect to specific properties different preparations of

<sup>14</sup> We were trying to further purify the tuberculin of Besredka, but our work was interrupted by unforeseen conditions preventing us from obtaining further supplies of tuberculin from Professor Besredka, and will be resumed as soon as possible. We wish at this time to express our appreciation to Prof. W. J. Gies for his valuable suggestions as to the methods to be employed in further chemical purification of the tuberculin.

tuberculin of Besredka vary markedly In trying to explain this variation in antigenic power in different samples of tuberculin, we naturally suspected the inequality of concentration of specific elements in respective preparations of tuberculin

In order to avoid this source of error we decided to isolate the protein fraction of tuberculin in each case by means of precipitation, and to use the equivalent antigenic doses for the test instead of diluting each tuberculin, as before, to the original volume

Ten cubic centimeters of each of Tuberculins II, III and IV were precipitated with two drops of glacial acetic acid Each precipitate was separated by centrifuging, suspended in 3 c c of salt solution and neutralized to phenolphthalein The resulting solutions were titrated for their antigenic values against several serums of active pulmonary tuberculosis by the regular complement deviation method The results are shown in Table 3

Having thus obtained the respective antigenic units of different samples of the coagulable protein fraction of tuberculins, we used in the subsequent tests equal antigenic values of each, namely, in case of Tuberculin II, 0.03 c c, in case of Tuberculins III and IV, 0.07 c c and 0.15 c c, respectively (about 5 antigenic units)

Although in general the results became more comparable than before, especially as the lipotropic reactions in Sample IV were absent, there were still a certain number of cases of tuberculosis in which (specially when the amount of antibody in the serum was not great) the reaction was positive only with either one or two of the three samples of tuberculin used

TABLE 4—THE COMPARISON OF THE OCCURRENCE OF FIXATION WITH DIFFERENT SAMPLES OF PURIFIED TUBERCULIN

	Results Obtained								Total Occurrence of Fixations		Total No of Cases
									Tubercu- losis Per Cent	Con- trols* Per Cent	
Sample of tuberculin	II	+	+	+	+	-	-	-	92	8	
	III	+	+	-	-	+	-	+	88	8	
	IV	+	-	-	+	+	+	-	36	2	
Cases of diagnosed tuberculosis		18	26	2	0	0	0	0	4		50
Controls*		2	5	1	0	0	0	1	91		100

\* In this number are included cases in which the infection with tuberculosis was not suspected at the time of the test

That the differences shown in Table 4 in the frequency of the occurrence of fixation with different samples of tuberculin were not due to faults of technic was shown by the fact that the same results were obtained in repeated examinations

Each case in which the findings obtained by different antigens did not coincide was reexamined repeatedly, and only such cases were included in the table in which repeated examinations revealed the permanent character of the discrepancy. In view of the fact that the possible differences in the amounts of specific constituents in respective samples of tuberculin were eliminated by purification and subsequent titration, the variations in antigenic efficiency recorded above can be explained only on the basis of *qualitative differences inherent in the specific constituents* of respective samples of tuberculin.

If we seek causes that account for the evident differences in apparently similar samples of Besredka tuberculin, several possible answers suggest themselves. Since the tuberculin consists of the culture medium in which tubercle bacilli have grown for a certain length of time (and there necessarily exist a number of possible variations affecting the rate of growth of different lots of cultures), different cultures are likely to contain variable amounts of the metabolic products of the organism. A further source of variation lies in the fact that in the process of preparation tuberculin is heated under pressure to kill the tubercle bacilli and some unrecorded variations in the heating process might cause partial destruction of the antigenic value of certain batches of the tuberculin.

#### THE STRAIN SPECIFICITY OF TUBERCULINS

As we have stated previously,<sup>9</sup> the complement deviation test with Besredka's tuberculin may be positive in cases in which no clinical evidence of tuberculosis could be found at the time of serological examination. In studying the question of fixation in such cases we used for control the von Pirquet test. We have shown that in all cases in which the serum test was positive the von Pirquet was also present, whereas many cases with a positive von Pirquet reaction, gave a negative serum test. In a number of cases in which the serum findings were the first to call attention to the possible presence of active tuberculosis, the subsequent histories of the cases have confirmed the early serological findings. However, in a number of cases in which this test was used there were many cases in which the subsequent study of patients was not possible and the positive serological findings in such cases remained unconfirmed by clinical data.<sup>9</sup>

In view of the foregoing findings, which show that in certain cases the positive findings with one sample of tuberculin may not be confirmed by examination with another sample of tuberculin of Besredka, we con-

sidered it interesting to study further the reliability of complement fixation test in clinically nontuberculous cases

During the last twenty months we examined over 4,000 serums<sup>15</sup> Among this number in 232 instances we obtained positive findings with either one or two samples of the tuberculin of Besredka, when clinically tuberculosis was not suspected at the time of the serum test Each of the 232 serums thus selected was reexamined with the tuberculin of Besredka, and if the reaction obtained was invariably positive, each case was subsequently examined with seven different preparations of tuberculin<sup>16</sup> We found that in 167 cases (or 72 per cent) out of 232 the fixation was obtained also with at least four antigens out of seven used Of the remaining 65 cases in 23 at least two tuberculins fixed the complement and in 12 cases CTBH was the only one confirming the results obtained with the tuberculins of Besredka In 30 cases out of a total of 232 the fixation was obtained only with the tuberculins of Besredka

It is thus evident that among 232 cases in which tuberculin of Besredka caused the fixation of complement, in almost 87 per cent of the total number one or more of other tuberculins also fixed the complement The difference in frequency of occurrence of reaction with respective antigens in case of different serums is not due to technical error This is evident from the fact that in many instances in which the same serum happened to be examined repeatedly, the results of such examinations invariably agreed This permanent character of discrepancies in the results obtained by using various tuberculins suggests as the only possible explanation the existence of selective specificity of the tuberculous antibody

The specific nature of the selective fixation was especially apparent in cases in which the serum fixed complement only with the tuberculins containing human tubercle bacilli, or a mixture of human and bovine

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15 Each serum coming to the laboratory for any serological examination was also examined for tuberculosis

16 We used for this purpose the Crude Tuberculin of the Board of Health of New York (CTBH), "Old Tuberculin" Höchst (OTH), "Old Tuberculin" of Parke, Davis & Co (OTPD), "Old Tuberculin" of Mulford containing human TB (OTMH), "Old Tuberculin" Mulford containing bovine TB (OTMB), "Bacillary Emulsion" Parke, Davis & Co (BEPD) and our own polyvalent Bacillary Emulsion containing human as well as bovine TB (BEWPH) Each of the seven antigens was titrated against a serum from a case of active tuberculosis and their respective units were determined In the complement deviation test 5 units of each antigen were used

We take this opportunity to thank most sincerely Prof W H Park of the New York City Board of Health, as well as Dr E M Houghton of Parke, Davis & Co, and Dr A P Hitchens of Mulford Company, who kindly placed at our disposal large amounts of their tuberculins

strains, but not with the tuberculin "OTMB," for instance, containing only bovine strains. There were in our series, however, a number of cases which fixed the complement with this tuberculin, as well as with human, and in two cases we obtained the fixation only with bovine antigen, and not with human.

It is thus evident that there is in tuberculosis a certain degree of strain specificity and this contributes to the failure of certain tuberculins to answer the requirement for an antigen in the complement deviation test. The fact that different samples of the tuberculin of Besredka may differ in regard to the number of strains, and respective amounts of each, in given tuberculin preparations, would also account for the variations in antigenic values of Preparations II and III as observed above.

The amount of material at hand is not sufficient to allow of any classification of the tuberculins named, as to their comparative antigenic value, but even the results obtained already show that the antigen of Besredka may be of the greatest usefulness in the complement deviation test in cases of early nondiagnosed tuberculosis, as we have stated before,<sup>9</sup> especially if the number of strains composing tuberculin be further increased and the final product purified.

We have shown that out of 4,000 cases in which tuberculosis was not suspected at the time of the serum test, in 232 instances the complement deviation with Besredka's tuberculin was positive. We have shown, also, that such fixations were not due to a technical imperfection of the test, inasmuch as the fixation in these cases was obtained on repeated examinations. Moreover, we showed that in 202 out of 232 of such cases, complement fixations were obtained also by the use of other tuberculins. The question arises whether we shall consider the fixation in these cases as specific, especially in the thirty cases in which the antigen of Besredka was the only one to cause fixation.

Our previous studies<sup>4, 9</sup> of the subject showed that the value of this fixation is very suggestive, inasmuch as in many cases more careful subsequent examination revealed the presence of disease, and in several cases in which no clinical confirmation of serum findings could be obtained at the time, later—in the course of a year—many came to be considered tuberculous clinically. The results of the complement deviation test, however, *were not confirmed in all cases* by subsequent clinical observations.

One must not forget, however, that in the group of cases considered clinically as nontuberculous, are certainly a number of cases of latent and spontaneously cured tuberculosis. In fact, considering the results of injection of tuberculin, or the findings at necropsy, we may safely say that the majority of individuals, considered nontuberculous,

are not free from latent infection. And from this point of view it is very difficult to say with certainty whether the serum findings in such cases are correct or not.

There is only one way of controlling the serum findings in such cases with any degree of certainty, and that is by injecting tuberculin in all cases which come for serum diagnosis. But inasmuch as such procedure is not free from danger, we could not adopt it.

On the other hand, we noticed recently numerous reports on the incidence of urochromogen reaction in a large number of tuberculous individuals. In fact, according to some investigators, the reaction was even fine enough to permit following the progress of the treatment. As in our preliminary work<sup>17</sup> with this method we were not able fully to substantiate the optimistic findings of other workers, we decided to repeat the work in a larger number of cases.

Dombrowski<sup>18</sup> in 1907 determined the urochrome of the urine in health and disease. By his method of determination with copper, he found that in health there is excreted 0.3885 gm. in a twenty-four-hour specimen of urine, whereas in pneumonia and in typhoid fever this amount may be increased to 1.0572 gm. per day. Four years later Weisz<sup>19</sup> pointed out certain discrepancies in Dombrowski's results. According to this author the urochrome of Dombrowski is not identical with the normal urinary urochrome. On isolating this coloring matter from normal and pathological urines, he found that the cadmium salt of Dombrowski urochrome is insoluble in diluted acetic acid, whereas the normal urochrome is soluble in this acid.

According to Weisz, the normal coloring matter of the urine is derived from a chromogen which in its properties is similar to the proteic acids which are present in the urine. This urochromogen when present in the urine is the substance which is responsible for the Ehrlich diazo reaction. Again, according to Weisz<sup>20</sup> there are two distinct urochromogens, which he distinguishes as A and B. The B urochromogen gives the diazo reaction promptly. The A urochromogen, on the other hand, does not give this reaction in freshly voided urines. When, however, these urines are allowed to stand in the incubator for twenty-four hours or so, a positive diazo reaction will be given by the A urochromogen.

When these urochromogens are oxidized either by dilute solution of potassium permanganate or by iodine and potassium thiosulphate, they are changed to the true urochromogen of the urine.

In 1911 Weisz<sup>21</sup> reported the results of his six years' study of the urochromogen reaction in urines of patients suffering with pulmonary tuberculosis. He found that the test for urochromogen in these patients was positive in the great majority of cases. It is necessary, he said, in considering the diagnostic significance of this test, to exclude those other diseases which also yield a positive Weisz reaction. In this class he groups typhoid fever, measles, scarlet fever, septicemia, surgical tuberculosis, etc. He also found

17 Bronfenbrenner, Rockman and Mitchell. *Biochem Bull.*, 1915, xiii, 80.

18 Dombrowski. *Compt rend Acad d Sc*, 1907, cxlv, 575, *Ztschr f physiol Chem*, 1908, liv, 390.

19 Weisz, M. *Biochem Ztschr*, 1911, xxx, 333.

20 Weisz, M. *Med Klin*, 1911, vi, 1661.

21 Weisz, M. *Munchen med Wchnschr*, 1911, lviii, 1378.

that patients who had been narcotized, or who had received injections of tuberculin, gave positive results with this reaction. A positive reaction in tuberculosis may, according to Weisz, indicate either a low resistance to the tuberculous toxin, or a spreading lesion with an increasing production of toxin. A positive reaction is of unfavorable prognostic significance.

The destruction of tissue causing the excretion of the urochromogen also causes an increase in the output of neutral sulphur of the urine. The oxyproteic acid fractions with which the urochromogen seems to be closely related is normally present in the urine in small quantities. According to Bondzynski<sup>22</sup> and his pupils antoxyproteic acid is a mixture of the proteic acid with urochromogen.<sup>23</sup>

The destruction of tissue which liberates the increased quantities of proteic acids can be measured in several ways. These substances contain nitrogen and sulphur and are combined with urochromogen. Methods have been advanced, therefore, to study this substance, either by precipitation and nitrogen determination, or by precipitation and sulphur analysis, or by the urochromogen method.<sup>24</sup>

Paranhos and Grolito,<sup>25</sup> found that the Weisz reaction was positive in 90 per cent of tuberculous patients. Cotton<sup>26</sup> obtained excellent results. Vitri<sup>27</sup> of Buenos Aires obtained positive reactions in patients in whom the tuberculin skin test was positive. He found that the presence of a little albumin, sugar or urobilin did not interfere with the Weisz reaction. Dozzi<sup>28</sup> as well as Pignacca<sup>29</sup> consider this test pathognomonic of tuberculosis. Curti<sup>30</sup> found that this test was positive in pneumothorax as well as in all cases of clinical tuberculosis. The reaction, according to this author, ran parallel with the clinical symptoms of the disease and became negative in cases which were, clinically, considered cured. Tecon and Aimart,<sup>31</sup> Jaquerod,<sup>32</sup> Kaplansky,<sup>33</sup> Puley<sup>34</sup> and others, have found this reaction of value. Similar results were obtained by Levy,<sup>35</sup> Heflebower,<sup>36</sup> Metzger and Watson,<sup>37</sup> Ferrannini,<sup>38</sup> Bruni,<sup>39</sup> Burgess<sup>40</sup> and Sinclair.<sup>41</sup>

22 Bondzynski Kosmos, 1911, xxxv, 650

23 Sklepinsky, A Pharm Centralbl, 1911, li, 615

24 In fact, according to Weisz the interdependence between the appearance of excess of neutral sulphur in the urine and the incidence of urochromogen reaction is so great that he is inclined to take the positive outcome of urochromogen test for an indicator of the presence of excess of neutral sulphur in the urine. It is in this sense that we identified in our first paper (Bronfenbrenner, Rockman, and Mitchell, Biochem Bull, 1915, No 13, p 80) the findings of urochromogen with the sulphur, although the Weisz reaction per se is, of course, not the test for neutral sulphur, but for urochromogen.

25 Paranhos and Grolito, V Brazil med, 1913, xxvii, 101

26 Cotton, E Rev méd de la Suisse romande, 1913, xxxiii, 217

27 Vitri, G Semana méd, 1913, xx, 110

28 Dozzi, L Gazz d osp, 1913, xxxiv, 815

29 Pignacca, G Gazz d osp, 1914, xxxv, Nos 34-35

30 Curti Quoted in Munchen med Wchnschr, 1914, p 1577

31 Tecon and Aimart Presse méd, 1914, p 135

32 Jaquerod Discussion, Presse med, 1914, p 135

33 Kaplansky Discussion, Presse méd, 1914, p 135

34 Puley Munchen med Wchnschr, 1915, xxvi, 1009

35 Levy Deutsch med Wchnschr, 1915, xli, 1212

36 Heflebower Am Jour Med Sc, 1912, cxliii, 221

37 Metzger and Watson Jour Am Med Assn, 1914, lxi, 1886

38 Ferrannini Riforma med, 1915, xxxv, 479

39 Bruni Gazz d osp, 1915, xxxvi, 401

40 Burgess Jour Am Med Assn, 1916, lxi, 82

41 Sinclair Jour Am Med Assn, 1916, lxi, 247



The technic of the Weisz reaction is very simple. Several cubic centimeters of urine are diluted two or three or more times to reduce the intensity of the color of the urine. To this are then added several drops of a 0.1 per cent solution of potassium permanganate. In the presence of the urochromogen a deep yellow color appears.

All told we examined 1,046 cases, of which number 681 were the conditions in which the increased output of neutral sulphur was not suspected, and the remaining 365 cases were classified as follows:

TABLE 5—REACTIONS IN VARIOUS DISEASES

	Number of Cases	Diazo		Weisz		Percentage Positive	
		Pos	Neg	Pos	Neg	Diazo	Weisz
Typhoid	67	32	35	18	49	47.7	26.9
Diabetes	58	1	57	9	49	1.7	15.5
Cancer	67	0	67	4	63	0	5.9
Tuberculosis	173	14	159	22	151	8.0	12.7
Unclassified	681	43	638	63	613	6.3	9.9
Total	1,046	90	956	121	925	8.6	11.5

From these results we are led to the conclusion that the Weisz reaction is not always incident in diseases characterized by tissue destruction. In 365 cases of such diseases which are characterized by marked protein katabolism, only fifty-three positive urochromogen reactions were obtained.

Moreover, when present, this reaction is not pathognomonic of tuberculosis, in fact, as the table shows, the percentage of incidence of urochromogen reaction is even higher in diabetes, and especially in typhoid, than in tuberculosis. The high incidence of urochromogen reaction in different pathological conditions was shown before in cancer,<sup>42</sup> diabetes,<sup>43</sup> pneumonia,<sup>44</sup> cachexia,<sup>45</sup> and in typhoid.<sup>46</sup> For instance, Halbey<sup>47</sup> found that the urochromogen test was positive in nine cases of typhoid at each application of the test so long as the fever kept up. It was positive in all cases of measles, scarlet fever,

42 Goodridge, F. G., and Kahn, M. *Biochem. Bull.*, 1915, iv, 118.

43 Einhorn, M., Kahn, M., and Rosenbloom, J. *Arch. f. Verdauungskr.*, 1911, xvi, 557.

44 Mancini. *Deutsch. Arch. f. klin. Med.*, 1911, ciii, 288.

45 Mazzitelli. *Riforma med.*, 1912, xxviii, Abstr. *Jour. Am. Med. Assn.* 1913, lix, 978.

46 Kuhl, A. *Deutsch. med. Wchnschr.*, 1915, xxi, 912.

47 Halbey, K. *Med. Klin.*, 1915, xi, 830.

erysipelas and malaria. It was constantly negative, on the other hand, in seventeen cases of pulmonary disease, even in advanced forms, and negative, likewise, with miliary tuberculosis. A positive reaction was thus obtained in 33 per cent of the fifty-two patients tested.

The high figures for positive Weisz reaction that have been reported by a number of observers in various diseases and especially in tuberculosis, may be due to the fact that atypical color reactions were considered as indicative of a positive test. When dilute potassium permanganate solution is added to the urine there is frequently noticed a pinkish tinge, which, unless care is taken and a standard prepared with which comparisons can be made, may be erroneously interpreted as an indication of the presence of urochromogen.

It is evident from the results reported in Table 5 that the urinary examination cannot be used as a safe control in serum diagnosis of tuberculosis. For, on the one hand, the urochromogen reaction is found to be positive only in about 13 per cent of cases of tuberculosis, in which the serum reaction is positive usually in about 92 per cent of cases, and, on the other hand, the frequent occurrence of this reaction in conditions other than tuberculosis makes valueless the findings of 10 per cent of positive reactions in nonclassified cases, as far as diagnosis of tuberculosis is concerned. The actual relationship between the two reactions, however, can be judged only by performing both tests in the same cases. This we did in 212 cases, with the results shown in Table 6.

TABLE 6—COMPARISON OF UROCHROMOGEN AND SERUM REACTIONS

			Serum Test	Tub Bacilli Present	Weisz Reaction Present	Percentage of Occurrence	
						Serum	Weisz
Lung tuberculosis	Stage I	Serum test positive	21	1	1	84 *	4
		Serum test negative	4				
	Stage II	Serum test positive	31	15	1	94	94
		Serum test negative	2	2	2		
	Stage III	Serum test positive	2	2		15.3	30.7
		Serum test negative	11	11	4		
No tuberculosis clinically		Serum test positive	7	0	3	1.9	7.8
		Serum test negative	134	0	8		

\* We do not offer at present any definite explanation for the comparatively low number of positive findings in this series, but it is evident that at least three causes could well explain it: (1) the mistaken diagnosis, (2) absence of resistance on the part of the patient (Bronfenbrenner, *J. Science*, 1914, *xxiv*, 804, also *Proc. Soc. Exper. Biol. and Med.*, 1914, *xi*, 92), (3) the known fluctuation in the antibody content in the blood of recently infected individuals (see discussion by Meyer, *Deutsch. med. Wochenschr.*, 1914, p. 513).

The examination of Table 6 reveals the fact that the urinary findings do not go parallel with serum findings. On the contrary, whereas the serum findings, very high in primary and secondary stages of pulmonary tuberculosis, falling very markedly in the tertiary stage of the disease, the urinary findings seem to show a marked increase in frequency as the disease progresses.

Although as Table 5 has shown, the katabolic changes in the body are not always followed by the presence of urochromogen in the urine, it is evident that there is undoubtedly an increased incidence of urochromogen reaction in later stages of the destructive process as compared with the earlier stages of the same disease. This increase in the incidence of Weisz reaction together with the corresponding inverse changes in the occurrence of the serum test, may be of great value in confirming our previous conclusion that cases of clinical tuberculosis in advanced stages in which the serum reaction is negative are characterized by the loss of resistance on the part of the patient<sup>17</sup>. In these cases the destructive processes develop more rapidly, which is indicated by the large excess of neutral sulphur in the urine, as well as by a high percentage of positive urochromogen findings. As for the seven cases of positive serum findings out of the total of 141 cases in which tuberculosis was not suspected, the urinary analysis does not offer any possible way of controlling the diagnostic value of these findings. As we have mentioned before, however, we do not feel inclined to attribute such findings to the possibility of nonspecific fixation, but rather to the fact that in its earlier stages the tuberculous process does not induce symptoms sufficient for clinical diagnosis. This is why a number of cases may present at necropsy unmistakable symptoms of a tuberculous process having taken place at some time during the life of the person without his being aware of the presence of the disease.

#### CONCLUSIONS

Attempts to study further the value of biological methods of diagnosis of tuberculosis led us to the following conclusions:

Different samples of tuberculin of Besredka, though apparently identical in the mode of their preparation, may differ among themselves in their specific values.

The most striking variation is in the amount of lipins contained in tuberculin.

It is necessary to free each sample of tuberculin of all its lipin fraction before using such tuberculin for the complement deviation test.

The lipins may be extracted by fat solvents, but the easiest method was found to be that of separation of the protein fraction by precipitation.

Precipitation of the antigenic fraction of tuberculin also offers the possibility of using a standard number of units of antigen and thus eliminating variations due to the quantitative differences in specific properties of different samples of tuberculin, without increasing the chance of obtaining lipotropic reactions

It seems, however, that different samples of tuberculin may vary also qualitatively

The variation rests apparently on the fact of the existence of strain specificity in the antibody

The existence of strain specificity in tuberculosis may explain why the results obtained by different investigators in the complement deviation test for diagnosis of tuberculosis vary so much

The tuberculin of Besredka seems to give the best results in diagnosis by the complement deviation test

Even though the test is positive in a certain number of clinically non-tuberculous cases, the reaction seems to be specific

In at least 87 per cent of such cases the fixation was obtained also with one or more preparations of tuberculins other than that of Besredka

The attempt to control serum findings by the urinary examination for urochromogen was not successful in general, because we were unable to confirm the frequent occurrence of the Weisz reaction in tuberculosis. A comparison of the frequency of occurrence of the two reactions in different stages of the disease suggests that negative serum findings in the face of the positive Weisz reaction may have an unfavorable prognostic significance

#### ADDENDUM

Since the above material was reported, our attention has been called to the article of Craig (*American Journal of the Medical Sciences*, 1915, cl, 781), in which the author gives a simple method of preparation of antigen for the complement deviation test for the diagnosis of tuberculosis. The results obtained by Craig are in general in accord with those obtained by us with the antigen of Besredka. Indeed, they are even more encouraging than ours.

In one respect, however, our respective results seem to differ in a marked degree, that is, in the percentage of positive reactions obtained among syphilitics. In our series about 20 per cent of all syphilitics reacted with the antigen of Besredka, whereas in the series of Craig, the occurrence of tuberculosis among syphilitics as judged by this test was less than 1 per cent. As we stated at the time, the comparatively high percentage of positive reactions among syphilitics in our series was not due to nonspecific fixations. In fact in cases in which such study was undertaken, we invariably found the two specific antibodies coexisting independently. We came to the conclusion, therefore, that the comparatively frequent simultaneous occurrence of the two reactions is due to the fact that tuberculosis is more frequent among syphilitics than among the persons free from luetic infection. It seems that syphilitic infection makes the person less resistant to a subsequent infection with tuberculosis, or at least renders him less resistant against the progress of tuberculosis previously contracted. Such a conclusion is apparently borne out by

clinical observations of such men as Fournier, C F Marshall, Douty, F H Andrews, Sir Jonathan Hutchinson, and others (see *Oxford System of Syphilis*, 1914, III, 197)

The fact, however, that in the series of 150 syphilitics Craig obtained a positive complement fixation with his tuberculin in only two cases, speaks at the first glance against such a conclusion. But if one takes into consideration that the material of Craig must have consisted largely or entirely of strong young men of military age, the difference can be explained easily. In our series of syphilitics we dealt with men or women of all ages, mostly working people, greatly exposed to infection with tuberculosis in their factory surroundings, and even more so in the unhealthy conditions of their life in the slums. Craig's material consisted of a group of men who must have been comparatively free from tuberculosis at the time of admission to military service, and who, in addition, having been admitted to service, were placed in conditions of life which are exceptionally favorable for assisting the person in resisting any possible preexisting tuberculous infection and sheltering him from any possible new infection. We therefore think that our previous statement about the frequency of occurrence of tuberculosis among syphilitics is correct, if the syphilitics are taken from a group of persons the same as that from which the rest of our material was derived.

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# TWO ADDITIONAL CASES OF MILIARY TUBERCULOSIS OF THE PLACENTA WITH CLINICALLY LATENT TUBERCULOSIS OF THE MOTHER \*

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The two cases of placental tuberculosis which form the subject of this report are of unusual interest, for in each the disease was so slightly active as to be unrecognized clinically in the mother, but was found in the course of the routine microscopical examination of the placenta. In one instance no history suggestive of tuberculosis could be elicited and the disease, apparently incipient during pregnancy, has become latent since the birth of the child. This case, therefore, is similar to the one reported from this laboratory in 1913 by Dr. Warthin,<sup>1</sup> in connection with which he at that time called attention to the increased importance of the sociologic and eugenic aspects of the transmission of tuberculosis from parent to child, provided that it can be shown that in women who have incipient or clinically unrecognizable tuberculosis the bacilli may enter the blood stream and cause a miliary tuberculosis of the placenta or congenital infection of the fetus.

The second case to be reported is in some respects even more unique. In this instance, also, the maternal tuberculosis was clinically unrecognizable at the time of admission to the hospital and was found only through the discovery of miliary tubercles in the course of the routine examination of the placenta. This patient, however, had wilfully falsified in regard to her history in order to conceal an earlier diagnosis of tuberculosis. This she admitted when she was told of the finding of placental tuberculosis. Unlike the first case and the one recently reported by Dr. Warthin, this woman's tuberculosis became more active after the birth of the child and she returned to the hospital with unmistakable clinical signs of pulmonary tuberculosis.

Without including here a review of the literature, attention is called to the fact that the reported cases of placental tuberculosis may be arranged in three groups:

1. Cases in which the mother was known to be tuberculous and in which, as a result of this knowledge, the placenta was given intensive

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<sup>1</sup> From the Pathological Laboratory of the University of Michigan

<sup>1</sup> Warthin, A. S. Miliary Tuberculosis of the Placenta. Jour. Am. Med. Assn., 1913, lxi, 1951

study and found to exhibit the characteristic lesions of tuberculosis, either with or without a demonstration of the bacilli

2 Cases in which the mother was known to be tuberculous and in which the presence of tubercle bacilli in the placenta or the fetal blood was demonstrated by staining methods or by animal inoculation without the recognition of the lesions of tuberculosis in the placenta. One must believe that in many of these cases the failure to find lesions was due either to unfamiliarity with the somewhat varied microscopical picture of placental tuberculosis, or to the fact that the amount of placental tissue examined in section under the microscope was such a small proportion of the total organ that characteristic lesions were not included

3 Cases in which the maternal tuberculosis was clinically unrecognizable and in which characteristic histopathologic lesions of tuberculosis were found in the routine examination of the placentas. In this group fall the two cases forming the subject of this report, the only other case in the group being the one reported by Dr Warthin, to which reference has been made

That three such cases should be found in one laboratory and within the space of three years is strong additional argument, not alone for the belief that the maternal transmission of tuberculosis is much more common than is ordinarily taught, but also for the little recognized fact that a "subclinical" tuberculosis may be so influenced by pregnancy that bacilli may enter the blood stream and produce placental or fetal miliary tuberculosis

#### REPORT OF CASES

Summaries of the histories of the two cases here reported follow

CASE 1—Miss K, aged 21, entered the maternity ward of the University Hospital, service of Dr Reuben Peterson, April 23, 1914. The patient was then in about the eighth month of pregnancy. There was no history of tuberculosis in her family, father, mother and eight brothers and sisters being alive and well. One sister died in childbirth. On physical examination by Dr Seeley the patient was found to be of slight build but fairly well nourished. No signs of any pulmonary lesion were discovered and the examination of the heart was likewise negative. The findings in the routine ante partum obstetrical examination do not concern us here. The Wassermann reaction was reported negative by one serologist and positive (one plus) by another. Blood and urinary findings were negative.

June 11, the patient was delivered by Dr Bartholomew of an apparently healthy female child. The puerperium was uneventful and the patient returned to her home June 27. The child was left at the University Hospital until July 16. It was then 35 days old, had gained 550 gm, and was apparently normal in all respects.

The placenta from this birth was placed in formol after being securely tagged with the name of the mother. It was sent to the pathological laboratory and in the course of the routine microscopical examination miliary tubercles were found. These lesions will be described later.

In October, 1915, the family physician of this patient, replying to an inquiry addressed to him by Dr Loomis, said that both mother and child were under observation, were apparently well and had given no evidence of tuberculosis at any time.

CASE 2—Mrs C, aged 27, was admitted to the obstetrical wards of the University Hospital, service of Dr Peterson, Jan 28, 1914. She was then in the ninth month of pregnancy. The patient denied any family history of tuberculosis, saying that her father, mother, three brothers and two sisters were living and well. Two sisters died in childhood. Concerning her personal history she said that she had never been strong until the past few years, but that she had made a good recovery from measles and scarlet fever in childhood and also from "congestion of lungs and bowels" five years previously. The patient was married nine years before and had one child, aged 7. There had been no other pregnancies.

The history of the present pregnancy presented nothing unusual. There had been considerable nausea and vomiting in the second and third months, but little afterward. No eye symptoms or dizziness, no swelling of ankles, no headache had occurred.

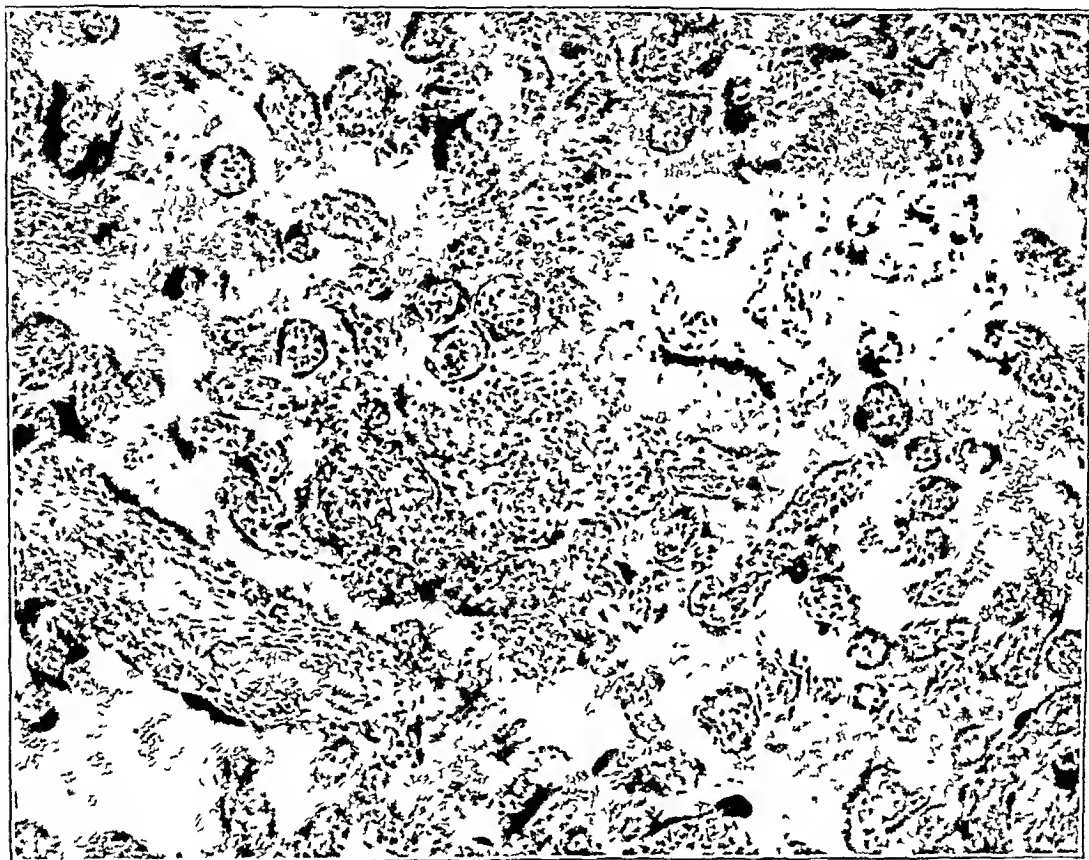


Fig 1—Miliary tuberculosis of the placenta. Clinically latent tuberculosis of the mother. In the center of the field an intervillous epithelioid tubercle.

On physical examination, made by Dr Loomis Jan 30, 1914, the patient was found to be of a rather large frame, with musculature and panniculus good. Face pale but conjunctivae and lips of good color. Eyes reacted normally to light and accommodation. Neck, mouth and throat were negative. The thorax presented marked infra- and supraclavicular fossae and was found to be somewhat larger and to move more freely on the left than on the right side. The lung borders had a wide excursion. Resonance was normal. The breath sounds were likewise normal except for occasional piping râles, and the voice sounds were generally, but uniformly increased. It was noted that the patient had some cough, and accordingly fine crackling râles were carefully sought for but were not heard. Auscultation and percussion of the back gave only negative findings.



The routine antepartum examination of breasts, abdomen and pelvis need not be detailed. There was no indication that the confinement would be otherwise than normal. Such proved to be the case, and Mrs C was delivered rather precipitately Feb 4, 1914. The child was an apparently healthy male weighing 7 pounds, 1 ounce. The puerperium was normal throughout and the history of the child was uneventful during the fourteen days that it remained in the hospital. At the expiration of this period the mother took the child to her home in a distant part of the state.

The placenta from this birth was placed in 10 per cent formaldehyd solution at once and delivered to the pathological laboratory March 8, 1914. In the routine microscopical examination of this placenta there was found a group of four or five miliary tubercles. The microscopical findings will be described in greater detail later.

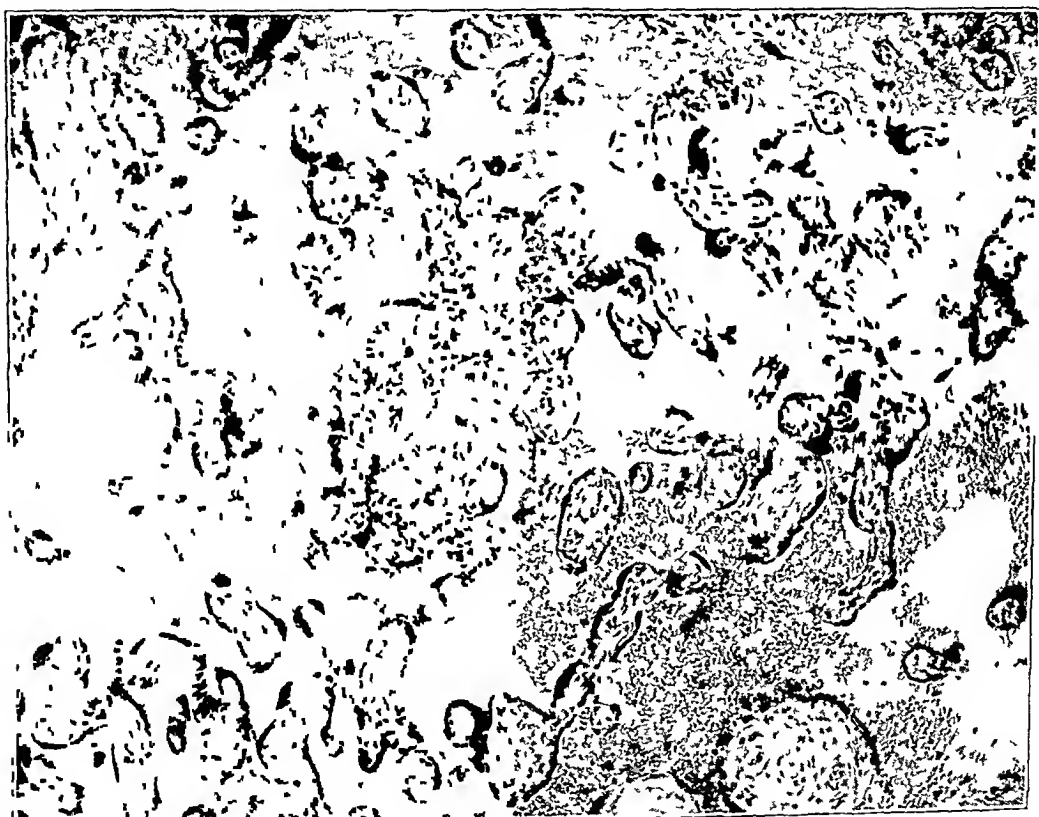


Fig 2—Miliary tuberculosis of the placenta, Case 2. Pulmonary lesion unrecognizable during pregnancy, but becoming active after birth of child. An intervillous epithelioid and giant-cell miliary tubercle.

In January, 1915, letters of inquiry were sent to Mrs C and to her home physician asking for additional information as to a possible history of tuberculosis (although the patient had stated that there was no history of tuberculosis in the family), and also in regard to the condition of both mother and child. The reply of the mother was especially interesting, throwing, as it did, much light on the subsequent history of the case and revealing an altogether too common attitude on the part of the patient. Mrs C's letter follows in part:

"I am very glad to be able to send you a favorable report, also glad to know you are interested enough in us to write and inquire. Baby is strong and well and has never been sick enough to call a doctor."

"As to my own health, I am well and strong as can be. I have had perfect health ever since I left the hospital. I understand that Dr. Peterson wrote to our doctor here, saying that at the time of the baby's birth you found signs of tuberculosis. I am not at all surprised as I have been told before that I had tuberculosis but I did not believe it, so thought I would not speak of it and *let you find it if you could*. I lay our good health all to fresh air, for we are fresh air fiends."

The patient's home physician kindly wrote under date of Jan 19, 1915, saying that Mrs. C had a history of tuberculosis dating back some eight or ten years. He had not had an opportunity to examine mother or child since her confinement, but as far as he could learn they were apparently well. Five months later (June 30, 1915) her physician again wrote, saying that Mrs. C was losing weight rapidly and apparently doing badly, although no active pulmonary focus was discovered. The baby remained in "excellent condition." Because of this information the patient was advised to return for examination, which she did July 26, 1915, entering as an outpatient, the service of Dr. A. W. Hewlett, through whose kindness the notes taken at that time were placed at my disposal. The patient then disclosed her earlier history of pulmonary tuberculosis. She said that she had had pneumonia in the right lung six years previously, after which she did not recover strength and was told that she had tuberculosis. Accordingly she went West for three years, but returned apparently perfectly well.

In the seventeen months which had elapsed since the birth of her child, the patient had been well, except for some cough and sputum, until the beginning of the summer, when she began to grow weak and tired and to raise more sputum. The following April she had pain in the right upper chest, at some times dull and radiating to the scapular region, and at other times knife-like in character, keeping her awake at night. She had been taking her own temperature at 4 p. m. each day but had had no fever except for a period of about one month, when she had noted an afternoon temperature 2 to 3 degrees above normal. During that month she was very tired so that she had to go to bed most of the time, but more recently she had felt stronger. There had been a loss of weight of 20 pounds in the previous six months.

In examining the patient at this admission, Dr. Hewlett found increased fremitus in the right scapular region and beneath the inner end of the right clavicle. Sharp crackling râles, brought out by coughing, were occasionally heard in the interscapular region. A diagnosis of pulmonary tuberculosis was made.

The lesions discovered microscopically in the placentas of these two patients are in every respect characteristic and there can be no doubt that they are miliary tubercles. Without a detailed discussion of the histopathology of placental tuberculosis (which may be found in the papers of Schmorl and Geipel<sup>2</sup> and Warthin<sup>3</sup>), attention is called to the fact that the differential diagnosis of placental tubercles presents but few difficulties if the lesions are present in at least moderate numbers and have not reached a stage of advanced healing. This point has been emphasized by Warthin,<sup>1</sup> and he has shown that even when the tubercles have advanced to a healing stage the two other things which need to be considered in differentiation are essentially unlike them. In small localized areas of *syphilitic chorioamnionitis* the process involves only the stroma

2 Schmorl and Geipel. *München med. Wchschr.* 1904, 1: 1676.

3 Warthin. *A. S. Jour. Infect. Dis.*, 1907, 1: 347.

of the villi and the villi are not fused into a solid fibroblastic or fibroid mass. In the small *healing infarct* the villi may be fused, but there is no fibroblastic formation, or only the slightest, between them. In the *healing tubercle*, on the other hand, if villi are fused in the mass, there is an abundant intervillous epithelioid or fibroblastic proliferation.

#### MICROSCOPICAL FINDINGS

The original sections made in the routine examination of *Case 1* each showed four or five young and active miliary tubercles. Examination of other sections has shown that the distribution varies somewhat, but no section examined from this case has failed to disclose at least one tubercle. These tubercles are practically all in about the same stage, showing an active epithelioid proliferation without caseation, although some of the larger ones reveal a slight karyorrhexis and diffusion of chromatin. Giant cell formation was not noted. In regard to location, a large majority of the tubercles are intervillous, often involving within the mass four or five villi the outlines of which may still be made out around the periphery of the tubercle. Fewer intravillous tubercles are found and these correspond in their young epithelioid character to those just described. Earlier stages were not found, so that the bacilli must have been given off some time before delivery, and most of them at about the same time.

The original section from which the diagnosis of placental tuberculosis was made in *Case 2* showed a group of four or five intervillous miliary tubercles which were epithelioid in character. Study of a large number of sections from this case shows the total number of tubercles to be much smaller than in *Case 1*, many sections containing none, and but rarely more than one to a section being found. Although various stages are present, in general these tubercles are somewhat older than those of *Case 1*. None, however, show healing, but typical Langhans' giant cells are frequently seen, and in some instances there is an early fibroblastic proliferation. As in the first case, intervillous tubercles greatly predominate over those of other locations.

It is to be regretted that it is technically impossible to demonstrate tubercle bacilli in the lesions in these placentas. They were both intensely fixed in formol, which always makes the differential staining of the tubercle bacillus very difficult and often impossible. We are not alone in this experience as it is mentioned in various works on microscopic technic and constitutes one of the many objections to the routine use of formol as a fixing agent. We believe, however, that our inability to demonstrate the bacilli does not in the least detract from the value of these cases for the lesions are absolutely characteristic, they differ in no respect from similar lesions in other cases in which the bacilli have been demonstrated in large numbers, and in one of the two cases here presented, the diagnosis of tuberculosis has been supported in an unusual way by the subsequent development in the mother of an active pulmonary process.

As far as can be ascertained, there has been no evidence of tuberculosis in either of the children from these births. Whether this is due to the fact that the bacilli were of relative slight virulence, or that they

passed the placenta in too small numbers to determine a clinically recognizable infection, or whether the fetal tissues offered more than ordinary resistance, can only be conjectured

#### SUMMARY

The two cases of placental tuberculosis here presented were discovered in the routine microscopical examination of the placentas. The mothers did not have clinically recognizable lesions at the time of delivery, but in one case an active pulmonary tuberculosis later developed. The other case became latent after the birth of the child. These cases are additional proof of the fact that even an incipient and unrecognizable tuberculosis may be so influenced by pregnancy as to cause a placental, and therefore potentially a fetal, miliary tuberculosis.

My thanks are due Dr. A. S. Warthin, who made the original diagnosis of placental tuberculosis in these cases, for placing the material at my disposal, to Dr. Reuben Peterson and Dr. A. W. Hewlett for the use of the records of their respective departments, and to Dr. F. L. Loomis of the Department of Obstetrics and Gynecology for his assistance in following up the after-history of the cases.

## PROGRESSIVE LIPODYSTROPHY \*

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A few years ago I had under observation at different times two girls aged 10 and 12 years, respectively, in whom I was struck by the marked contrast between the emaciated face with hollow cheeks and the good development of the rest of the body. These children were brought to the clinic for slight ailments and were not affected with any constitutional disease. I realized that I was dealing with a rare condition, but was at a loss to know where to search for a description of it in the literature. A paper recently published by Feer<sup>1</sup> on "Lipodystrophia Progressiva" immediately cleared up the diagnosis. Unfortunately no detailed history, photographs or measurements were taken at the time, and the patients are no longer under observation.

I had the good fortune recently to discover a typical example of this condition in the person of a mother who brought her children for treatment. The history is briefly as follows:

### REPORT OF CASE

*History*—Mrs. K., aged 32, Hebrew, has been married for ten years to her cousin. She had three brothers and two sisters. One sister died in childhood of pneumonia. One brother and the sister are married and have healthy children. No other member of the family has had a similar condition, neither the mother of the patient nor the other female members were unusually fat or thin, nor did any one have an increased amount of adipose tissue in the lower part of the body. There is no family history of syphilis, tuberculosis, alcoholism, diabetes or nervous diseases. The birth was normal, the patient was breast fed, and her physical and mental development during childhood was normal. At the age of 3 she had measles without complications. Since that time, with the exception of occasional headaches, her health has always been good. The change in her face was first noticed at the age of 6. It began insidiously, without any fever, pain or discomfort, and gradually became more marked, so that at 11 the fat of the face had almost entirely disappeared. Later the dystrophy spread to the neck, upper part of the chest and arms, so that these parts became distinctly thinner. When she was 11 years old the family emigrated from Russia to this country. The patient was taken to a well known New York physician, who after a careful examination told the mother that he hoped her other children were as healthy. The patient began to menstruate at 13 years. She married at 22 years, her weight at that time was 44.5 kg (98 pounds). After her marriage she began to notice that the lower part of her body was growing stouter, and this continued, so that at the age of 28 she weighed 53.5 kg (117 pounds) and at 31 years 55.5 kg (121 pounds). Except for the disfiguring appearance of her face, she has not suffered in any way, her appetite is good, her

\* Submitted for publication Jan. 27, 1916.

1 Feer: *Lipodystrophia Progressiva*, *Jahrb. f. Kinderh.*, 1915, LXXXII, 1.

bowels regular, she has no disturbances of sleep, no palpitation or nervous symptoms. She has two children, a girl aged  $8\frac{1}{2}$  years, who is perfectly healthy, and a boy aged 7 years, who has chronic endocarditis following an attack of rheumatism. She has had no miscarriages or stillbirths, and is now pregnant for the third time. Both children were breast fed for one year.

*Physical Examination*—Measurements weight, before pregnant, 55.5 kg, in seventh month of pregnancy, 59 kg, height, 150 cm, circumference of the head, 53 cm, neck, 31.5 cm, chest, 80 cm, arm, 22 cm, elbow, 21.5 cm, forearm, 21.5 cm, thigh (at level of great trochanter), 62 cm, at 15 cm above patella, 53.5 cm, knee, 36.5 cm, leg, 37.5 cm, ankle, 23 cm, thickness of the raised fold of fat and skin—cheek, 5 mm, breast (over nipple), 6 mm axilla (level of nipple), 6 mm, interscapular region, 8 mm, arm, 5 mm, forearm, 5 mm, neck, 7 mm, thigh, 45 mm, leg, 27 mm.

One is immediately struck by the disproportion between the upper and lower parts of the body. The face is haggard, and has a cadaverous expression (Fig 1). It is hollowed in the temporal region, the malar bones are prominent, and below them there are two hollows, an upper small one, and a lower large one



Fig 1—Progressive lipodystrophy in a woman of 32 years. Author's case

separated by a thin bridge, corresponding to the zygomatic muscle. This renders the masseter more distinct, and gives a fulness around the corners of the mouth. There are also distinct grooves under the lower lip and on either side of the chin. When the patient smiles, folds form on both sides of the mouth. The neck shows a marked reduction of the subcutaneous fat, also the arms and upper part of the trunk. There is no disturbance of function or sensation in these parts. Examination of the hair, eyes, ears, nose, throat and teeth shows nothing abnormal. The patient does not complain of flushing, profuse perspiration or chilliness. The breasts are well developed and on account of the small amount of subcutaneous fat are unusually hard. Examination of the heart and lungs shows normal conditions. From the crests of the ilia downward there is a very marked increase in adipose tissue, this is most distinct in the gluteal region and on the outer side of the thighs. It is less distinct on the leg and the ankle is not at all enlarged. The function of the muscles, sensation and the tendon reflexes are normal. Examination of the blood and urine shows nothing abnormal. The roentgenologic examination of the arm and of the skull (sella turcica) shows nothing pathological.

*Number of Cases, Race, Sex*—Up to the present, fifteen cases of progressive lipodystrophy have been reported by the following authors Barraquer,<sup>2</sup> Campbell,<sup>3</sup> Hollander,<sup>4</sup> Simons,<sup>5</sup> Laignel-Lavastine and Viard,<sup>6</sup> Cohn,<sup>7</sup> Lewandowsky,<sup>8</sup> Weber,<sup>9</sup> Christiansen,<sup>10</sup> Feer,<sup>11</sup> and Pic and Gardère.<sup>12</sup> In most of these reports a detailed history and measurements are not given. Three cases in males which are somewhat doubtful are reported by Shaw,<sup>12</sup> Hertz and Johnson,<sup>13</sup> Husler.<sup>14</sup> The condition is probably not as rare, however, as the figures would seem to indicate, for like other uncommon conditions, it is sometimes not recognized because not known. A number of the patients were Hebrew, though there does not seem to be any marked predisposition of the race to this condition. All of the undoubted cases have been in females, but it is not at all certain that males may not be occasionally affected.

*Etiology and Pathogenesis*—In those few instances in which the family history is given, there is no indication of any inherited tendency, either to the same condition or to a disturbance of the fat metabolism. Syphilis, tuberculosis and alcoholism apparently play no part in the causation of this condition. In those patients in whom the Wassermann test was made the result was uniformly negative. The patients may of course be affected with intercurrent diseases, but these apparently bear no relation to the underlying condition, which appears to be a form of trophoneurosis. One naturally thinks of some disturbance in the function of one or more of the ductless glands, but symptoms of hyperthyroidism such as palpitation, tremor, tachycardia, those of hypothyroidism, such as mental and physical sluggishness, subnormal temperature, constipation, are absent. Symptoms pointing to a disturbed function of the pituitary, supra-renals or ovaries are likewise absent. The condition occurs in married and in unmarried women, they present no unusual disturbances of menstruation, pregnancy or lactation. In addition, none of the patients has received any benefit from the administration of the extracts of the ductless glands. It is not unlikely that

2 Barraquer Abstr Neurol Centralbl, 1907, p 1072

3 Campbell Tr Clin Soc London, 1907, xl, 272, Proc Roy Soc Med, London, 1913, vi, 71

4 Hollander Ztschr f d ges Neurol u Psychiat, 1911, v, 633

5 Simons Ztschr f d ges Neurol u Psychiat, 1911, v, 29, *Ibid*, 1913, xix, 377, Ztschr f Kinderh, 1915, xi

6 Laignel-Lavastine and Viard Nouv iconog de la Salpetriere, 1912, xxv, 473

7 Cohn Abstr Neurol Centralbl, 1913, xxxii, 779

8 Neurol Centralbl, 1913, xxxii, 866

9 Weber Brit Med Jour, 1913, p 1154

10 Christiansen Mentioned by Feer, Note 1

11 Pic and Gardère Lyon med, 1909, cxiii, 61

12 Shaw Tr Clin Soc London, 1905, xxxviii, 222

13 Hertz and Johnson Proc Roy Soc Med, London, 1913, vi, 92

14 Husler Ztschr f Kinderh, 1914, x, 116

something in the circulating blood is the causative factor. The symmetrical, bilateral character would seem to indicate this. The fact that only certain parts of the body are affected, would not be a strong argument against such an assumption, for it is well known that certain organisms, toxins and other substances have a special affinity for certain tissues, and it is not impossible to conceive of a substance that would cause a diminution or disappearance of the fat in one part of the body and an increase in another part. By injecting the blood of patients in



Fig 2—Progressive lipodystrophy in a woman of 21 years. Simons' case

the *active progressive stage* of the disease into monkeys it might be possible to produce somewhat similar changes.

*Symptoms and Course*—The loss of the subcutaneous fat of the face begins insidiously without fever, pain or other symptoms and gradually becomes more marked, it is bilateral and symmetrical. In six of the patients, including my own, the disease began between the fifth and the seventh year; in the remainder, about the time of puberty. In the majority of the cases the loss of subcutaneous fat then extended



to the neck, arms and upper part of the trunk. The orbital fat is little if at all affected and as no postmortem examinations have been made, it is still unknown whether the internal fat is diminished. The increase of adipose tissue in the lower part of the body begins or becomes more marked at the time of puberty. This increase is most distinct in the gluteal region and on the outer side of the thigh, but also involves the rest of the leg. As a rule, both sides are equally affected, occasionally the increase is greater on one side. The amount of subcutaneous

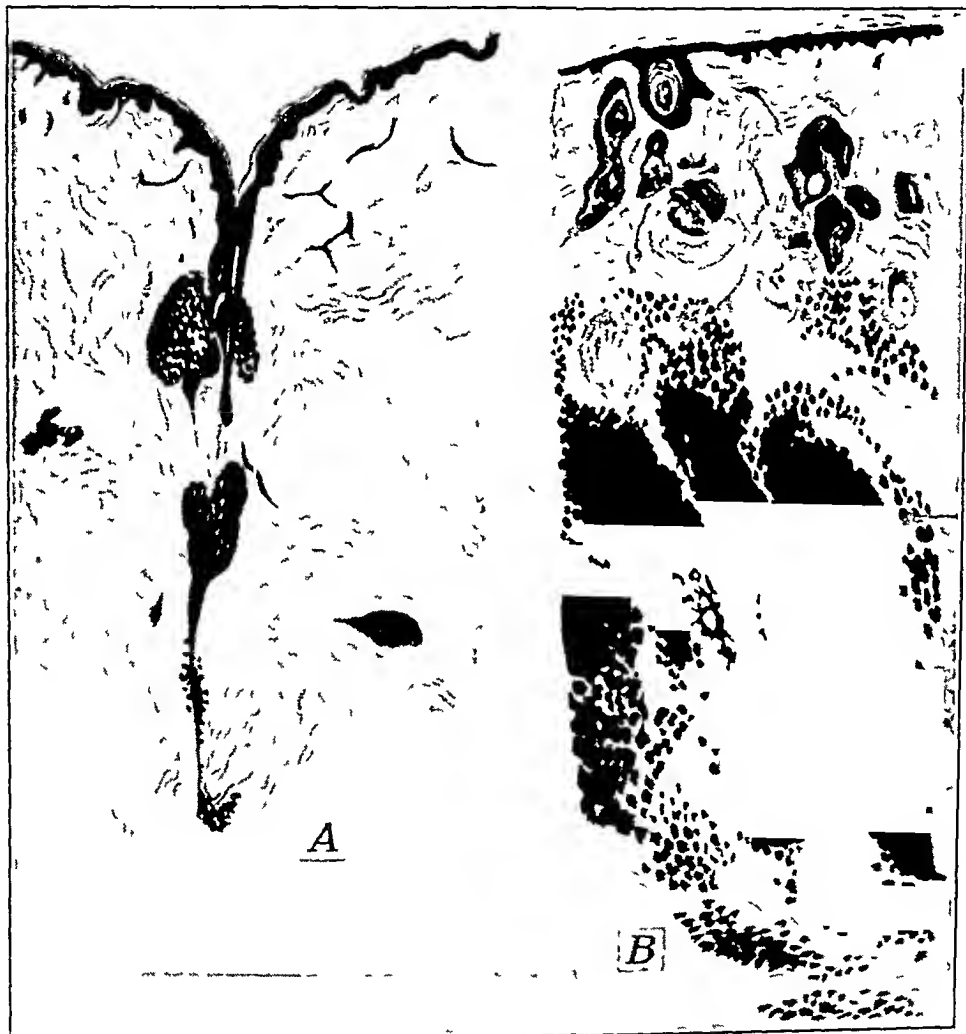


Fig 3—Microscopical sections. A Progressive lipodystrophy. Skin removed to the fascia, almost complete absence of fat, traces in the sebaceous glands and at the roots of the hair. B Fat content of the normal skin of the head in man 34 years old. Both specimens stained with hematoxylin-Sudan (Simons').

fat gradually increases, but after a certain number of years probably remains stationary, so that, strictly speaking, the disease can no longer be considered progressive. The examination of the parts affected shows no impairment of function of the muscles, no change in the electrical reactions of the muscles or nerves, or in the tendon reflexes, no

disturbances of sensation, no vasomotor disturbances. Roentgenologic examination of the extremities and the skull (sella turcica) shows nothing abnormal. The measurements in the seven cases in which they are given are as shown in Table 1.

TABLE 1—MEASUREMENTS OF SEVEN PATIENTS WITH LIPODYSTROPHY

Author	Circumference						
	Age, Years	Weight, Kg	Height, Cm	Arm, Cm	Forearm, Cm	Thigh, Cm * †	Leg, Cm
Simons	21	46.8	158			56	
Simons	28	56.0	159			61 51.5	37.5
Laignel Lavastine and Viard	33	53.0	150	22	20	56 46.0	36.0
Cohn	17					57 53.5	39.0
Feer	9½	26.9	130	16.5	15.5	36.0	26.5
Boissonas	7½	22.1	119	17	18.0	34.5	26.5
Herrman	32	55.5	150	22	21.5	62 53.5	37.5

\* Measured at the level of the great trochanter

† Measured 15 cm. above the patella

The measurements of the thickness of the fold of raised skin and subcutaneous fat,<sup>15</sup> as first suggested by Oeder,<sup>16</sup> and carried out on children by Batkin,<sup>17</sup> are given by only three authors as set forth in Table 2.

TABLE 2—MEASUREMENTS OF THICKNESS OF FOLD OF SKIN AND SUBCUTANEOUS FAT

Author	Age, Years	Cheek, Cm	Breast, Cm	Avilla, Cm	Arm, Cm	Fore arm, Cm	Thigh, Cm	Leg, Cm
Laignel Lavastine	39						64	59
Feer	9½	4	3	3.5	3.5	2.5	30	18
Herrman	32	4	6	6.0	5.0	5.0	15	27

In none of the patients were changes found in the internal organs which could be attributed to the disease. The examination of the blood

15 The measurement of the thickness of the layer of subcutaneous fat is made as follows. A fold of skin with the subcutaneous fat is raised from the underlying muscle and held by an assistant between the thumb and index fingers of both hands, the thumbs being separated 3 or 4 cm. This double layer of skin and fat is then measured with a pair of calipers, not the kind which are used for measuring the diameters of the head or pelvis, but the kind used by mechanics. This touches the fold along a larger surface and the thickness can be more accurately determined.

16 Oeder. *Med. Klin.*, 1910, p. 17; *Fortschr. d. Med.*, 1911, p. 41.

17 Batkin. *Jahrb. f. Kinderh.*, 1915, LXXXII, 103.

and the urine, and the roentgenologic examination have shown no characteristic changes. In those cases which were tested no disturbance of metabolism and no vasomotor or trophic disturbances were noted. Three hundred grams of grape sugar have been given without producing an alimentary glucosuria, no increase of lipase has been found in the blood, after the ingestion of 200 gm of a 20 per cent cream there was no lipemia, the blood serum obtained by puncture of a vein was clear. When large quantities of cream and butter were taken the feces

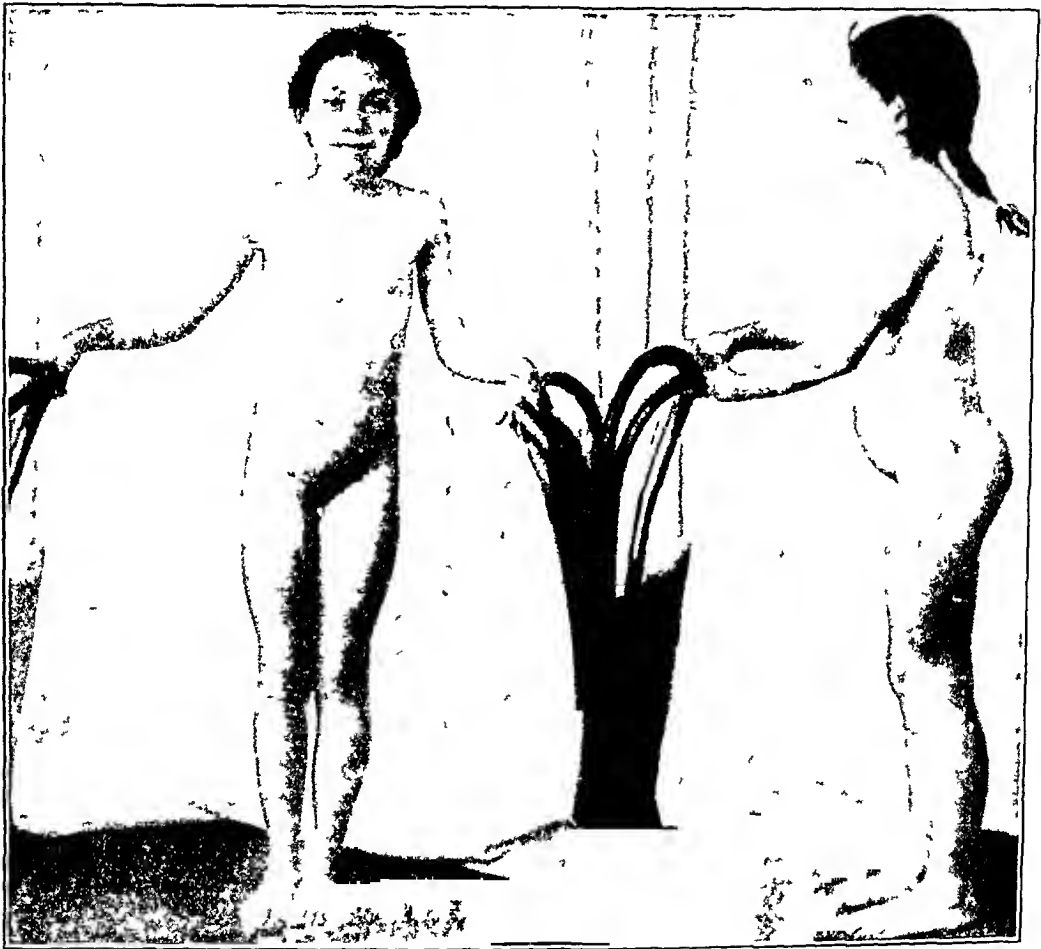


Fig 4—Boissonas' case, a girl aged 10. Disappearance of subcutaneous fat in the face, arms and chest, marked increase in the gluteal region, abdomen, hips and calves.

did not show any marked change. Injections of pilocarpin produced moderate sweating, less distinct on the face, the pulse, respiration and intestinal peristalsis were not affected.

Macroscopically a section of the skin of the affected part shows a marked diminution or a complete absence of fat, microscopically (Simons' Fig 3) almost a complete loss of the subcutaneous fat only in the sebaceous glands and at the roots of the hair can traces of fat be seen. The epithelium and the corium present no changes.

*Diagnosis and Differential Diagnosis*—If we bear in mind the characteristic features of this condition—bilateral, symmetrical loss of fat in the upper part of the body, with increase of adipose tissue in the lower part, and the absence of other trophic and constitutional disturbances—the diagnosis is usually easy. The cadaverous expression of the face in an otherwise healthy individual is almost pathognomonic. The good general health immediately excludes tuberculosis, malignant



Fig 5—Pulmonary tuberculosis in a girl 9 years old (Schlossmann)

tumors and diabetes. The retention of the normal function of the muscles excludes the various forms of muscular atrophy and dystrophy, the normal sexual characteristics and the absence of ocular disturbances separate it from dyspituitarism of the Froelich type.

In passing, it is interesting to note that in this disease the subcutaneous fat is lost in a location in which in infantile atrophy, even when extremely marked, it is retained, namely, as the fat or sucking pad of the cheek. On the other hand, in some cases of advanced pulmonary tuberculosis in children the fulness of the face may persist after the rest of the body is greatly emaciated (Fig 5). It is not uncommon

to see girls and young women in whom there is a striking contrast between the thinness of the face and the normal or more than normal development of the lower part of the body, and although I do not believe that such cases should be included in the group of progressive lipodystrophy, they may possibly bear some relation to that condition

*Prognosis*—Although the disappearance of the subcutaneous fat of the face is progressive, after it has all been lost the process must of necessity come to a standstill. A spontaneous reappearance of the fat is extremely unlikely. The increase in adipose tissue in the lower part of the body is also progressive, but after a certain number of years apparently reaches its maximum. The disease appears to interfere in no way with the general health, and it is doubtful if life is shortened.

*Treatment*—Thyroid, pituitary, and ovarian extract have been tried without benefit. Feer proposes to use the milk of a thyroidectomized goat, with which he obtained good results in a case of Graves' disease. The rationale of this method of treatment is not clear, since no similar disturbances have been noted in this disease. It would seem more logical to inject the blood of a patient in the active progressive stage of the disease into monkeys with the idea of stimulating the production of antibodies and later to inject the serum of such animals into the patient.

The patients are all female and naturally complain, chiefly, of the disfigurement, especially if they are still unmarried. For cosmetic reasons human fat and mutton suet have been injected into the hollows of the face, but after a time this is absorbed. Transplantation of the excess fat from the buttocks to the face has been suggested, but it is doubtful whether that will remain unabsorbed. Paraffin injections have been objected to because they interfere somewhat with the play of the features, but in view of the great deformity this does not appear a strong objection, and this is the method which I intend to employ in my patient.

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# A STUDY OF THE BUFFER VALUE OF THE BLOOD †

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In order that the various functions of the body may be properly performed, it is essential that the blood maintain its slightly alkaline reaction within extremely narrow limits. When this degree of alkalinity is diminished, a condition of acidosis, with its accompanying phenomena, is observed. A truly acid reaction of the blood (that is, a hydrogen-ion concentration greater than  $\text{pH-}7.0\ddagger$ ) is incompatible with life.

Various protective mechanisms serve to maintain the acid-base equilibrium of the organism and thereby protect the blood from significant changes in hydrogen-ion concentration. Such processes are increased production of ammonia, the excretion of carbon dioxide by the lungs, the excretion of nonvolatile acids by the kidneys, and finally, the buffer action of the blood itself.<sup>1</sup>

By the term "buffer action" of a mixture is meant its ability to take up considerable amounts of acid or alkali when these are added to it, without appreciable change in hydrogen-ion concentration. The blood is such a buffer mixture, owing largely to its content of carbonates and phosphates, and, to a lesser extent, its protein.

Much valuable work has been done to determine the rôle played by each of the factors concerned in the maintenance of acid-base equilibrium, but a precise investigation<sup>2</sup> of the "buffer value" of the blood has not been undertaken, owing to technical difficulties. The utilization of the recently-described dialysis-indicator method<sup>3</sup> for determining variations in the hydrogen-ion concentration of the blood has made possible a quantitative study of its buffer value.

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† From the Medical Clinic of the Johns Hopkins Hospital.

‡ pH is the commonly accepted symbol for hydrogen-ion concentration.

1 For a detailed discussion of the mechanisms involved in the maintenance of acid-base equilibrium in the body, see Henderson, L. J., *Ergebn d. Physiol.*, 1909, viii, 254.

2 During the course of this study a preliminary communication on "The Nature and Detection of Diabetic Acidosis," by Van Slyke, Stillman and Cullen, appeared in the *Proc. Soc. Exper. Biol. and Med.*, 1915, xii, 165. The fact that the dialysis-indicator method was being utilized for determining the buffer value of the blood was announced with the presentation of our method before the Association of American Physicians May, 1915. (See *Tr. Assn. Am. Phys.*, 1915, and abstract in *Jour. Am. Med. Assn.* 1915, lvi, 2162.)

3 Levy, R. L., Rowntree, L. G., and Marriott, W. McKim. A Simple Method for Determining Variations in the Hydrogen-Ion Concentration of the Blood, *THE ARCHIVES INT. MED.*, 1915, xvi, 389.

## TECHNIC

The determinations may be carried out on whole blood, serum or plasma, but it is preferable to use whole blood, since in this way conditions in the body are most closely approximated

Two cubic centimeters of blood are placed in each of seven test tubes and allowed to stand for five or six minutes, until a thin layer of plasma at the top has been cleared of cells, hemolysis on the subsequent addition of acid and alkali thereby being prevented. The blood in the first tube is used for a determination of the pH. To each of the next three tubes is added fiftieth-normal hydrochloric acid—0.1 cc to the first, 0.2 cc to the second, and 0.3 cc to the third. Similarly, increasing amounts of fiftieth-normal sodium hydroxid solution are added to the last three tubes. The tubes are inverted once for the purpose of mixing. Each portion of blood is then separately dialyzed for six minutes against 25 cc of 0.8 per cent salt solution and the pH of the dialysate determined by adding 5 drops of an indicator, phenolsulphonephthalein, the reading being determined by comparing with a series of standard colors

Numerous experiments were<sup>4</sup> carried out to determine the influence of various factors on the results

1 *Effect of Temperature*—The dialysate at temperatures ranging from 18 to 37 C may be identical or may show slight changes,<sup>4</sup> but within these extremes, no essential change is seen in the buffer value of either blood or serum. The determinations can, therefore, be carried out at room temperature, without regard for the slight variations so encountered

2 *Length of Time Elapsing Between the Withdrawal of Blood and the Carrying Out of Determinations*—The blood may be kept for as long as twenty-four hours without change in the pH or buffer values, providing it is collected in hard glass tubes which are filled to the top, tightly stoppered, and immediately placed on ice

3 *Length of Time the Acid or Alkali is in Contact with Blood or Serum*—A series of experiments was carried out in which the time of contact varied from two to thirty minutes. Within these limits, identical buffer values were obtained in all cases

4 *Loss of Carbon Dioxid*—Obviously, the carbon dioxid tension in the blood is important. Control experiments, using the dialysis-indicator method with carbon dioxid at its normal tension, and with blood from which carbon dioxid had been shaken out, showed marked differences in pH. It is possible to collect the blood in such a way that the loss of carbon dioxid is minimal and fairly constant. This is accomplished by withdrawing blood with a syringe or pipet, filling the test tube practically to the top, promptly stoppering, avoiding unnecessary shaking, and placing immediately on ice. Duplicate determinations on the same sample, or on different specimens from the same individual, yield essentially identical results under these conditions

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<sup>4</sup> Levy, Rowntree and Marriott, loc cit, note 3. The time of exposure to a higher temperature is obviously a determining factor

## MODE OF EXPRESSION OF RESULTS

All results are expressed in terms of cubic centimeters of fiftieth-normal hydrochloric acid or sodium hydroxid per 2 c c of blood. The following terms are used

1 *Buffer for Acid or Alkali*—These represent the amounts of acid or alkali which can be added to blood or serum without change in the pH of the dialysate<sup>5</sup>. The sum of the buffer for acid and that for alkali yields the *total buffer*.

2 *Reserve Buffer for Acid or Alkali*—These represent the amounts of acid or alkali which can be added to blood or serum without causing a change in the pH of the dialysate beyond the limits of normal<sup>6</sup>. The sum of the two yields the *total reserve buffer*. The reserve buffer, therefore, represents the simple buffer value *plus* the amount of acid or alkali taken care of by the blood without change in reaction beyond the limits of normal pH values. From a clinical standpoint it is the simple buffer values for acid and alkali which are of the greatest significance.

## ANALYSES OF CLINICAL RESULTS

The work is based on a study of sixty-five cases, involving considerably more than 100 buffer determinations. The results may best be presented by dividing the cases into four groups.

1 *Normal Individuals (Twenty-Four Cases)*<sup>7</sup>—Determinations were made on both blood<sup>8</sup> and serum, the results appearing in Tables 1 and 2. It is noteworthy that the time elapsing between the previous meal and the withdrawal of blood for examination made no essential difference in the buffer values.

(a) *Blood*—Normal blood takes 0.1 c c of acid or alkali without change in pH. It, therefore, has a buffer for acid and alkali of at least 0.1, though it may have a buffer of 0.2 to 0.4. The average buffer, both for acid and alkali is 0.18. The total buffer ranges from 0.2 to 0.7, with a group average of 0.36.

The reserve buffer<sup>9</sup> for both acid and alkali varies from 0.1 to 0.4, the group average for the acid being 0.27, that for the alkali 0.31. The total reserve buffer varies from 0.4 to 0.7, the group average being 0.58.

(b) *Serum*<sup>10</sup>—Normal serum always takes 0.1 c c of acid without change in pH. It may have a buffer for acid of from 0.1 to 0.3, the

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5 No attempt was made to determine changes smaller than 0.05.

6 Normal pH values are: Blood, 7.4 to 7.6, Serum, 7.6 to 7.8.

7 The blood on which these determinations were made was obtained from patients in the Genito-Urinary Dispensary, a majority of whom were under treatment for local infections of the lower genito-urinary tract. No licit individuals are included in the series.

8 The blood was collected in tubes containing just sufficient carbonate-free sodium oxalate to prevent clotting.

9 The reserve values throughout are not absolute since in many instances 0.3 c c of acid and alkali failed to carry the pH beyond normal limits.

10 The values for oxalated plasma are essentially the same as those for serum. Throughout the later studies only whole blood was utilized for the following reasons: 1 In the body it is with the buffer of the blood as a whole with which we are concerned. 2 Less blood suffices. 3 Centrifugalization together with the resultant loss of carbon dioxide is avoided.



TABLE 1—NORMAL CASES

Case No	Blood								Serum								Time Elap sing Since Last Meal, Hours		
	pH	N + $\frac{N}{50}$ HOI (cc)				N + $\frac{N}{50}$ NaOH (cc)				pH	N + $\frac{N}{50}$ HOI (cc)				N + $\frac{N}{50}$ NaOH (cc)				
		01	02	03	04	01	02	03	04		01	02	03	04	01	02		03	04
1	7.6	7.6	7.55	7.5	7.6	7.7	7.8	7.8	7.8	7.7	7.6	7.5		7.8	7.95	7.95	8.2	1 3/4	
2	7.55	7.55	7.45	7.45	7.55	7.55	7.65	7.65	7.7	7.7	7.6	7.5		7.7	7.9	8.0	8.0	2	
3	7.6	7.6	7.5	7.45	7.6	7.6	1.65	7.7	7.7	7.7	7.55			7.7	7.8	7.8	7.9		
4	7.5	7.5	7.35	7.3	7.5	7.55	7.6		7.7	7.7	7.65	7.6		7.7	7.8	7.95	7.95	6	
5	7.55	7.55	7.45	7.45	7.55	7.55	7.65	7.7	7.7	7.7	7.63	7.55		7.9	7.95	8.0	8.05	2	
6	7.55	7.45	7.35	7.3	7.55	7.55	7.55	7.55	7.7	7.7	7.53	7.55		7.8	7.9	7.95	8.0	2	
7	7.45	7.45	7.45	7.3	7.45	7.45	7.6	7.55	7.7	7.7	7.65	7.5		7.7	7.95	8.0	8.1	1 1/4	
8	7.65	7.45	7.35	7.3	7.55	7.6	7.6	7.6	7.7	7.7	7.6	7.45		7.7	7.9	7.95	8.0	1 1/2	
9	7.55	7.53	7.45	7.45	7.55	7.55	7.65	7.65	7.7	7.7	7.6	7.5	7.75	7.9	7.9	8.0	8.0	2 1/2	
10	7.45	7.45	7.3	7.25	7.45	7.55	7.55	7.55	7.7	7.7	7.55	7.45		7.7	7.9	7.95	8.0	2	
11	7.45	7.45	7.35	7.25	7.45	7.45	7.55	7.55	7.7	7.7	7.53	7.45		7.7	7.9	7.9	7.9	2 3/4	
12	7.45	7.45		7.35	7.45	7.45	7.5	7.5	7.65	7.65	7.45	7.45	7.65	7.75	7.95	8.0		1 3/4	
13	7.45	7.45	7.45	7.35	7.45	7.45	7.45	7.45	7.65	7.65	7.45	7.35		7.75	7.85	8.05		2	
14	7.45	7.45	7.35	7.35	7.45	7.5	7.55	7.55	7.65	7.65	7.43	7.35		7.85	7.85	8.05		2	
15	7.45	7.45	7.35	7.35	7.45	7.45	7.5	7.55	7.65	7.65	7.45	7.45		7.8	7.8	7.85		2	
16	7.45	7.45	7.4	7.35	7.45	7.55	7.55	7.55	7.8	7.8	7.55	7.45		7.8	7.8	7.9		2 1	
17	7.45	7.45	7.4	7.4	7.45	7.55	7.7	7.7 1	7.7	7.7	7.65	7.55		7.8	7.9	8.05		5	
18	7.45	7.45	7.4	7.35	7.45	7.55	7.65	7.7	7.65	7.65	7.45	7.35		7.8	7.9	7.9		2	
19	7.45	7.45	7.35	7.35	7.45	7.55	7.65		7.75	7.75	7.6	7.5		7.9	7.9	8.1		3	
20	7.55	7.55	7.45	7.45	7.55	7.55	7.7	7.55	7.75	7.75	7.65	7.55		7.75	7.9	8.1		2	
21	7.55	7.53	7.55		7.55	7.55			7.65	7.65	7.55			7.75	7.75	7.8		2	
22	7.45	7.45	7.45		7.45	7.45	7.5		7.65	7.65	7.6	7.5		7.65	7.75	7.85			
23	7.45	7.45	7.45		7.45	7.45	7.55		7.65	7.65	7.55	7.55		7.65	7.75	7.75			
24	7.45	7.35	7.35		7.45	7.45	7.45		7.65	7.55	7.55	7.45		7.65	7.65	7.8			

average is 0.11. Its buffer for alkali is very variable, a change may be encountered on the addition of from 0.05 to 0.3 c.c. of fiftieth-normal sodium hydroxide, the average is 0.07. The total buffer for serum varies from 0.1 to 0.3, the group average being 0.18.

The reserve buffer for acid varies from 0.1 to 0.4, the group average being 0.2. The reserve buffer for alkali ranges from 0 to 0.3, the group average being 0.12. The total reserve buffer varies from 0.15 to 0.6, the average being 0.33.

TABLE 2—SUMMARY OF TWENTY-FOUR NORMAL CASES

		Blood		Serum	
		Extremes	Group Average	Extremes	Group Average
Buffer	For acid	0.2 - 0.4	0.18	0.1 - 0.3	0.11
	For alkali	0.2 - 0.4	0.18	0 - 0.3	0.07
	Total	0.2 - 0.7	0.36	0.1 - 0.3	0.18
Reserve buffer	For acid	0.2 - 0.4	0.27	0.1 - 0.4	0.2
	For alkali	0.2 - 0.4	0.31	0 - 0.3	0.12
	Total	0.4 - 0.7	0.58	0.15 - 0.6	0.33

TABLE 3—MISCELLANEOUS CASES WITH NORMAL pH AND NORMAL BUFFER VALUES, SIXTEEN CASES, TWENTY DETERMINATIONS

		Blood	
		Extremes	Group Average
Buffer	For acid	0.1 - 0.3	0.13
	For alkali	0.1 - 0.3	0.17
	Total	0.2 - 0.5	0.3
Reserve buffer	For acid	0.1 - 0.3	0.25
	For alkali	0 - 0.3	0.23
	Total	0.3 - 0.6	0.48

Although the total buffer value or the total reserve value may be great, the buffer for either acid or alkali may be small, in other words, the buffer may be great for acid and small for alkali, or vice versa. This can be determined only by actual study of the individual acid and alkali buffer values, and it is obviously not shown by a figure expressing the total buffer value.

2 *Miscellaneous Cases with Normal pH and Normal Buffer Values*—Twenty determinations were made on sixteen cases, including instances of diabetes mellitus, pernicious anemia, myeloid leukemia, typhoid fever, pregnancy, surgical cases before and after anesthesia, exophthalmic goiter and chronic nephritis (Table 3).

No	No			01	02	03	01	02	03	
1	33088	Intestinal parasitism, (Balantidium coli), marked anemia	4/22/15	7 45	7 45	7 45	7 7	7 75	7 75	Alveolar CO <sub>2</sub> tension, 28.6 mm., blood—R B O, 1,548,000, Hb, 20 per cent (Sahli)
2	34083	Bronchopneumonia	4/23/15	7 4	7 3	7 25	7 45	7 5	7 5	Alveolar CO <sub>2</sub> tension, 16.2 mm., extreme prostration with mental torpor, uremia suspected, died, necropsy showed no renal lesions
3	34693	Chronic nephritis, hypertension, albuminuric retinitis	9/10/15 10/ 7/15	7 45 7 55	7 45 7 55	7 45 7 55	7 65 7 55	7 65 7 7	7 65 7 75	Blood urea, 102 mg, phthalein test, 5 per cent in two hours, Ambard's K, 0.715 Blood urea, 78 mg, Ambard's K, 0.572
4	34753	Mercuricchlorid poisoning	9/24/15 9/27/15 9/28/15 9/29/15 10/ 6/15	7 6 7 55 7 7 7 65 7 5	7 55 7 55 7 7 7 65 7 5	7 15 7 55 7 65 7 55 7 45	7 6 7 65 7 7 7 65 7 6	7 65 7 75 7 75 7 75 7 65	7 65 7 75 7 85 7 8 7 65	Alveolar CO <sub>2</sub> tension September 23, 26.8 mm., fifth day since taking 7½ grain tablet, urine since Eighth day, voided 130 cc, anuria for seven days preceding, intensive alkali therapy Alveolar CO <sub>2</sub> tension, 33 mm., 485 cc urine voided, blood T N P, 173 mg Phthalein, 0 Ambard's K, 1.09, 1,185 cc urine voided Alveolar CO <sub>2</sub> tension, 30.6 mm., 1,770 cc urine voided, T N P N blood, 42 mg, phthalein, 27 per cent in two hours, Ambard's K, 0.186 Alveolar CO <sub>2</sub> tension, 39.1 mm., 2,120 cc urine voided, T N P N blood, 26 mg, phthalein, 33 per cent in two hours, Ambard's K, 0.124, recovered Alveolar CO <sub>2</sub> tension September 26, 22.8 mm., voluntary starvation, much acetone and diacetic acid in urine, getting sod blearb, 2 dr every four hours Before starvation, blood sugar, 0.13 per cent Starved for past four days, no alkali, Ambard's K, 0.112 blood urea, 29 mg Starved for seven days, no alkali, persistent glucosuria without hyperglycemia, acetone and diacetic acid in urine In coma, marked cyanosis, respiration labored, died same day
5	34685	Diabetes mellitus, chronic nephritis	9/24/15	7 15	7 35	7 35	7 55	7 55	7 55	Alveolar CO <sub>2</sub> tension September 26, 22.8 mm., voluntary starvation, much acetone and diacetic acid in urine, getting sod blearb, 2 dr every four hours Before starvation, blood sugar, 0.13 per cent Starved for past four days, no alkali, Ambard's K, 0.112 blood urea, 29 mg Starved for seven days, no alkali, persistent glucosuria without hyperglycemia, acetone and diacetic acid in urine In coma, marked cyanosis, respiration labored, died same day
6	34774	Diabetes mellitus (renal)	9/30/15 10/ 4/15 10/ 7/15	7 6 7 45 7 45	7 5 7 45 7 45	7 15 7 45 7 4	7 6 7 45 7 45	7 6 7 15 7 15	7 6 7 15 7 6	Alveolar CO <sub>2</sub> tension, 30.6 mm., 1,770 cc urine voided, T N P N blood, 42 mg, phthalein, 27 per cent in two hours, Ambard's K, 0.186 Alveolar CO <sub>2</sub> tension, 39.1 mm., 2,120 cc urine voided, T N P N blood, 26 mg, phthalein, 33 per cent in two hours, Ambard's K, 0.124, recovered Alveolar CO <sub>2</sub> tension September 26, 22.8 mm., voluntary starvation, much acetone and diacetic acid in urine, getting sod blearb, 2 dr every four hours Before starvation, blood sugar, 0.13 per cent Starved for past four days, no alkali, Ambard's K, 0.112 blood urea, 29 mg Starved for seven days, no alkali, persistent glucosuria without hyperglycemia, acetone and diacetic acid in urine In coma, marked cyanosis, respiration labored, died same day
7	34776	Cerebral arteriosclerosis, cerebral hemorrhage	9/30/15	7 45	7 45	7 45	7 5	7 55	7 55	Alveolar CO <sub>2</sub> tension, 30.6 mm., 1,770 cc urine voided, T N P N blood, 42 mg, phthalein, 27 per cent in two hours, Ambard's K, 0.186 Alveolar CO <sub>2</sub> tension, 39.1 mm., 2,120 cc urine voided, T N P N blood, 26 mg, phthalein, 33 per cent in two hours, Ambard's K, 0.124, recovered Alveolar CO <sub>2</sub> tension September 26, 22.8 mm., voluntary starvation, much acetone and diacetic acid in urine, getting sod blearb, 2 dr every four hours Before starvation, blood sugar, 0.13 per cent Starved for past four days, no alkali, Ambard's K, 0.112 blood urea, 29 mg Starved for seven days, no alkali, persistent glucosuria without hyperglycemia, acetone and diacetic acid in urine In coma, marked cyanosis, respiration labored, died same day
8	34831	Typhoid fever	10/14/15	7 5	7 5	7 45	7 6	7 6	7 6	Temperature at 2 p m, 103 F, ice sponge at 2 15, blood drawn at 2 40, patient having chill Temperature at 2 p m, 103 F, ice sponge at 2 15, blood drawn at 3 Acetone and diacetic acid in urine, has been getting CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
9	34845	Typhoid fever	10/11/15	7 45	7 45	7 45	7 55	7 6	7 65	Temperature at 2 p m, 103 F, ice sponge at 2 15, blood drawn at 2 40, patient having chill Temperature at 2 p m, 103 F, ice sponge at 2 15, blood drawn at 3 Acetone and diacetic acid in urine, has been getting CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
10	34869	Diabetes mellitus	10/26/15	7 55	7 15	7 15	7 65	7 65	7 65	Acetone and diacetic acid in urine, has been getting CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
11	34932	Acute tuberculous pneumonia	10/27/15	7 45	7 45	7 45	7 5	7 65	7 7	CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
12	34944	Bacillary dysentery	10/28/15	7 55	7 55	7 45	7 6	7 6	7 65	CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
13	G U	Hypertrophy of prostate, operation	11/ 3/15	7 45	7 45	7 4	7 15	7 55	7 55	CO <sub>2</sub> tension, 32.1 mm., blood sugar, 0.138 per cent Consolidation of entire right lung and part of left lung, respirations labored, rapid and shallow Prolonged diarrhea, 10 to 12 stools daily for several weeks, marked emaciation and weakness, died just before operation (control)
14	Obst	Pregnancy (9th mo)	11/ 4/15	7 4	7 35	7 3	7 1	7 1	7 1	Immediately after operation, perineal proctectomy, gas and ether (1 fl oz) anesthesia lasting 10 minutes
15	Obst	Pregnancy (9th mo)	11/ 4/15	7 45	7 45	7 15	7 5	7 55	7 6	Immediately after operation, perineal proctectomy, gas and ether (1 fl oz) anesthesia lasting 10 minutes
16	Bay View	Acute yellow atrophy of liver	11/17/15	7 15	7 15	7 15	7 55	7 55	7 55	Alveolar CO <sub>2</sub> tension, 34.1 mm Hg, in coma, died three days later, necropsy

\* The values of Ambard's coefficient, total N P N and urea were determined by the staff of the Chemical Division of the Medical Clinic to whom we are indebted for the privilege of using them. The nitrogen and urea figures represent mg per 100 cc. We desire to thank Dr J H King for a number of alveolar CO<sub>2</sub> determinations.

The values obtained are uniformly slightly lower than those observed in the series of normals, but otherwise present no features of especial interest

3 *Cases with Normal pH and Diminished Buffer Values* — (Tables 4 and 5) An analysis of these tables shows essentially normal buffer and reserve buffer values for acid, markedly diminished values for alkali, and therefore lowered values both for total and total reserve buffers

Several points of interest are evident from a consideration of this group of cases. It is striking that a diminished buffer for alkali is far more common than that for acid in cases which do not show a *true* acidosis, but in which there is a tendency toward acidosis, as evidenced in many instances by a lowering of the tension of the alveolar carbon

TABLE 5—CASES WITH NORMAL pH AND DIMINISHED BUFFER VALUES, SIXTEEN CASES, TWENTY-FIVE DETERMINATIONS

		Blood	
		Extremes	Group Average
Buffer	For acid	0 - 0.3	0.19
	For alkali	0 0.3	0.06
	Total	0 0.6	0.25
Reserve buffer	For acid	0 0.3	0.26
	For alkali	0 0.3	0.18
	Total	0.3 0.6	0.44

dioxid (Cases 1, 2, 4, 5, 10 and 16) The diminished buffer for alkali observed in two cases of normal pregnancy (Cases 14 and 15) is in accordance with the almost constant finding of a lowered alveolar carbon dioxid tension during the months of gestation<sup>11</sup>

Case 4 (mercuric chlorid poisoning) shows at various stages during the clinical course several phases of buffer loss. At first, after five days of anuria, there was loss of buffer for acid, with slight clinical improvement and the reestablishment of urinary secretion, buffer for acid returned, whereas that for alkali was diminished. After intensive alkali therapy, an alkalosis was established though the alveolar carbon dioxid was still somewhat lowered, the buffer values were normal. October 6, a slight set-back occurred, with loss of buffer for alkali. It was prognosticated at this time from the buffer determinations that the alveolar carbon dioxid tension, which two days previously had been normal,

<sup>11</sup> Lemdorfer, A. Novak, J. and Porges, O. *Ztsch f klin Med* 1912, 133: 301

TABLE 6—ACIDOSIS, NINE CASES, TWENTY-FOUR DETERMINATIONS

Case No	Medical No	Diagnosis	Date	Blood										Alveolar CO <sub>2</sub> Tension mm Hg	Remarks
				pH	N + $\frac{N}{50}$ HCl (cc)			N + $\frac{N}{50}$ NaOH (cc)							
					0 1	0 2	0 3	0 1	0 2	0 3					
1	33948	Acute and chronic nephritis, hypertension, uremia, albuminuria	4/20/15	7 35	7 35	7 35	7 3	7 6	7 6	7 65	10 4	Patient comatose, Ambard's K, 3 3			
			4/21/15	7 4	7 3	7 2		7 4	7 45			Died two days later, necropsy			
2	33799	Chronic nephritis, uremia	4/20/15	7 2	7 15	7 15	7 1	7 35	7 45	7 45		Ambard's K, 1 99, T N P N blood, 192 mg			
			4/21/15	7 15	6 9	6 9		7 15	7 25		11 0	Dull, nausea and vomiting, headache, died four days later, necropsy			
3	34066	Chronic nephritis, hydronephrosis (left), uremia, secondary anemia	4/21/15	7 05	7 0	6 9		7 15	7 2		0 0	Patient comatose, marked "air hunger", two hours later, given 500 cc blood by syringe transfusion and 400 cc 4 per cent sod bicarb intravenously, symptomatically unimproved, but at end of injection, pH of blood = 7 45, died with acute pulmonary edema four hours after the transfusion, Ambard's K = 3 68 ten hours before death, T N P N blood, 232 mg			
												T N P N blood, 181 mg			
4	34725	Chronic nephritis, hypertension, uremia, secondary anemia	10/ 4/15	7 35	7 35	7 3	7 15	7 35	7 4	7 45	25 0	Venesection for 650 cc blood on October 1			
			10/ 5/15	7 35	7 25	7 15	7 15	7 35	7 45	7 45	15 7	Given 300 cc 4 per cent sol sod bicarb + 200 cc 5 per cent glucose sol intravenously on this day, alveolar CO <sub>2</sub> tension immediately before injection, 11 mm, immediately after, 17 5 mm, marked "air hunger", respirations, 8 per minute, vomiting			
			10/ 7/15	7 35	7 3	7 0	6 9	7 45	7 45	7 55	11 0	Twenty four hours later, at this time given 400 cc of 4 per cent sol sod bicarb			
												Immediately after injection of the sod bicarb, respirations somewhat faster, still in coma			
			10/ 8/15	1 35	7 25	7 15	7 15	7 45	7 45	7 45		One and one half hours after alkali injection, breathing slow and labored, respirations 8 per minute			
				7 55	7 55	7 45	7 35	7 55	7 6	7 7					
				7 55	7 45	7 4	7 35	7 55	7 6	7 6					

5	G U	Ureteral kink, hydro nephrosis, opera tion	10/ 9/15	7 33	7 3	7 25	7 2	7 45	7 45	7 55		<p>Twenty four hours later, marked "air hunger", respirations, 12 per minute, in deep coma, at this time, given 300 cc of 4 per cent sod bicarb + 300 cc of a phosphate mixture (<math>\text{KH}_2\text{PO}_4 + \text{Na}_2\text{HPO}_4</math>) having pH of 7.4</p> <p>Immediately after the injection, no change in condition, died two hours later, urine alkaline throughout stay in hospital, pH 7.6</p> <p>Just before operation (Control) Patent in excellent condition</p> <p>Immediately after operation, cutting of aberrant vessels pressing on ureter, gas anes thesia lasting 1 hour and 35 minutes, uneventful postoperative recovery</p> <p>Comatose, marked "air hunger", blood sugar, 0.6 per cent</p> <p>Conscious, though mentally dull, during past twenty-four hours received about 1 oz of sod bicarb by mouth, and 500 cc of a saturated solution per rectum, died in coma two days later</p> <p>In coma, having repeated convulsions, phthalein, 12 per cent in two hours</p> <p>Mentally clear, much improved after sweating and bleeding</p> <p>Drowsy, though mentally clear, respirations rather deep, no "air hunger", blood urea, 16 mg, phthalein test, 42 per cent in two hours, blood sugar, 0.33 per cent</p> <p>Alveolar <math>\text{CO}_2</math> November 30 = 35.0 mm, starved, blood sugar, 0.25 per cent</p> <p>After intensive intravenous alkali therapy, still mentally dull, getting small amount of broth, green vegetables, and eggs, died two days later</p> <p>Marked "air hunger", stuporous, R B C, 1,800,000, Hb (Sahlb), 23 per cent, phthalin, 53 per cent in two hours</p> <p>Condition unchanged, died next day, necropsy</p>
6	31066	Diabetes mellitus, syphilis, aneurism of thoracic aorta	10/17/15	7 15	7 15	7 15	7 4	7 15	7 55	7 55	7 7	30 0
				7 35	7 35	7 2	7 2	7 35	7 35	7 4		28 0
			11/ 1/15	7 15	7 15	7 15	7 15	7 15	7 2	7 2	7 2	
			11/ 5/15	7 15	7 35	7 35	7 25	7 45	7 15	7 45	7 45	
7	33077	Acute and chronic nephritis, uremia	11/24/15	7 3	7 3	7 2	7 2	7 3	7 35	7 35	7 35	22 4
			11/27/15	7 15	7 15	7 45	7 45	7 65	7 65	7 65		
8	33078	Diabetes mellitus, hydronephrosis, chronic morphism	11/29/15	7 3	7 3	7 15	7 15	7 35	7 35	7 35	7 35	23 3
			12/ 5/15	7 35	7 3	7 15	7 15	7 35	7 35	7 35		19 5
			12/ 9/15	7 15	7 15	7 45	7 4	7 45	7 5	7 5		23 0
9	35034	Carcinoma of stom ach, large hepatic metastases, marked secondary anemia	12/10/15	7 35	7 35	7 15	7 15	7 35	7 35	7 15	7 15	12 1
			12/11/15	7 35	7 35	7 35	7 15	7 45	7 45	7 55	7 55	11 4

would be found to be again lowered, which, indeed, proved to be true. Finally, during convalescence, both pH and buffer values became normal.

The loss of buffer for alkali observed in two instances of febrile typhoid (Cases 8 and 9) is in accord with the tendency toward an alkalosis which we have observed in several cases of this disease.

• TABLE 7—ACIDOSIS, NINE CASES, TWENTY-FOUR DETERMINATIONS

	Blood					
	Acid		Alkali		Total	
	Extremes	Averages	Extremes	Averages	Extremes	Averages
Entire group (9 cases, 24 determinations)	0.03	0.083	0.03	0.087	0.04	0.17
During stage of true acidosis (9 cases, 16 determinations)	0.03	0.075	0.03	0.056	0.04	0.13
During stage of compensation (6 cases, 8 determinations)	0.03	0.1	0.03	0.1	0.103	0.2

TABLE 8—SUMMARY OF ACID, ALKALI AND TOTAL BUFFER VALUES FOR THE VARIOUS CASE GROUPS EXPRESSED AS GROUP AVERAGES

	Blood		
	Acid	Alkali	Total
Normal individuals	0.18	0.18	0.36
Miscellaneous cases with normal pH, showing normal buffer values	0.13	0.17	0.30
Cases with normal pH showing diminished buffer values	0.19	0.06	0.25
Acidosis	True	0.075	0.056
	Compensated	0.10	0.10

4 *Acidosis*—(Tables 6 and 7) From the tables it is evident that cases of acidosis have less buffer for both acid and alkali during the stage of uncompensated acidosis (increased pH of the blood) than during the stage in which the tension of alveolar carbon dioxide is diminished, but the pH of the blood is normal (stage of compensation). Despite the return to normal of pH and buffer values, the clinical evidences of acidosis may persist (Cases 4 and 8).

#### EXPERIMENTAL CONSIDERATIONS

Inasmuch as the buffer value of blood is fairly constant in health, and decreased in acidosis, the question obviously arises as to whether buffer can be supplied. The possibility of accomplishing this with

phosphate mixtures was considered. The buffer values of phosphate mixtures ( $\text{Na}_2\text{HPO}_4 + \text{KH}_2\text{PO}_4$ ) of various strengths and hydrogen-ion concentrations, were therefore determined, the results appearing in Table 9.

From this study four interesting facts are evident. First, the buffer value of blood is greater than that of  $\frac{1}{15}$  molecular phosphate mixtures and approximately that of  $\frac{1}{5}$  molecular mixtures, second, the buffer value is greater at neutrality than in more alkaline mixtures, third, the dialysates exhibit buffer values comparable to those obtained by adding the indicator directly to the original mixtures, but at a

TABLE 9—BUFFER VALUE OF PHOSPHATE MIXTURES ( $\text{Na}_2\text{HPO}_4 + \text{KH}_2\text{PO}_4$ )

	1/30 Molecular		1/15 Molecular	1/5 Molecular	
	Undialyzed	Dialysate	Undialyzed	Undialyzed	Dialysate
pH	7.55	7.4	7.3	7.5	7.45
+0.1 acid	7.45	7.35	7.2	7.5	7.45
+0.2 acid	7.4	7.25	7.15	7.45	
+0.3 acid	7.3	7.15	7.15	7.45	
+0.4 acid	7.2	7.1		7.4	7.35
+0.1 alkali	7.6	7.5	7.3	7.5	7.45
+0.2 alkali	7.75	7.65	7.35	7.55	
+0.3 alkali	7.8	7.75	7.4	7.55	
+0.4 alkali	8.0	7.8		7.6	7.6

ONE-FIFTEENTH MOLECULAR		ALL READINGS ON UNDIALYZED MIXTURES		
pH	7.05	7.3	7.0	8.1
+0.1 acid	7.05	7.2	7.85	7.95
+0.2 acid	7.0	7.15	7.75	7.85
+0.3 acid	6.95	7.15	7.7	7.75
+0.1 alkali	7.05	7.3	7.95	
+0.2 alkali	7.05	7.35	8.0	
+0.3 alkali	7.1	7.4	8.1	

uniformly more acid level, and, finally, the more concentrated the mixture employed, the less marked is the discrepancy between the undialyzed mixture and dialysate.

Attempts to increase the buffer value of the blood by intravenous injection of phosphate mixtures into animals and into a human case (Table 6, Case 4) failed, but demonstrated the following facts:

1. The phosphate mixtures are relatively nontoxic.



TABLE 10—Protocol of Experiment 1 Injection into a Dog of Third Normal Hydrochloric Acid, Followed by a 4 Per Cent Solution of Sodium Bicarbonate\*

MALE, WEIGHT, 86 KG

Time	Total Amount Injected (cc)		Blood						Alveolar CO <sub>2</sub> Tension, mm Hg	Remarks	
	N/3 HCl	4% NaHCO <sub>3</sub>	pH	N + $\frac{N}{50}$ HCl (cc)			N + $\frac{N}{50}$ NaOH (cc)				
				0.1	0.2	0.3	0.1	0.2			0.3
12 10	→		7.55	7.45	7.45	7.55	7.55	7.55	38.6	Dog on table respirations, 23 per min, pulse, 31 to 1/4	
12 25										Injection of HCl begun	
12 40	75		7.35	7.35	7.3	7.35	7.35	7.35	31.9	Breathing is slow and deep, salivating profusely, muscles relaxed, defecating involuntarily, seems much distressed, injection stopped	
12 46	150									Marked "air hunger", involuntary defecation continues	
12 50			7.15	7.1		7.15	7.2	7.2		Respirations, 16 per min, deep and irregular, pulse, 23 to 1/4	
1 00	155								27.1	The injection of the last 10 cc of acid immediately caused deepening and quickening of respiration	
1 05										Injection of NaHCO <sub>3</sub> begun	
1 07	165									Respirations decidedly shallower, animal still relaxed and quiet	
1 08	←										
1 14		85	7.35	7.3	7.2	7.4	7.15	7.45			
1 20									39.5	Animal more animated, struggling	
1 25		120							43.8	Free diuresis, pH of urine, 7.65	
1 35		250	7.6	7.5		7.6	7.6	7.6		Injection stopped	
1 40		350									
1 50		500									
2 05			7.7	7.6	7.6	7.7	7.8	7.8	48.0	Animal seems weak, breathing quietly, sacrificed	
2 12											

\* Injections made into leg vein, blood for examination withdrawn from jugulars, N/3 HCl made up in 0.8 per cent salt solution, bicarbonate solution made up in distilled water. Arrows mark beginning and end of injections.

TABLE 11.—PROTOCOL OF EXPERIMENT 2 INJECTION INTO A DOG OF A 4 PER CENT SOLUTION OF SODIUM BICARBONATE, FOLLOWED BY N/3 HYDROCHLORIC ACID \* MALL, WRIGHT, 625 KG

Time	Total Amount Injected (cc)		pH	Blood						Alveolar CO <sub>2</sub> Tension, mm Hg	Remarks
				N + $\frac{HCl}{50}$ (cc)			N + $\frac{NaOH}{50}$ (cc)				
	1% NaHCO <sub>3</sub>	N/3 HCl		0.1	0.2	0.3	0.1	0.2	0.3		
10.00			7.35	7.35	7.3	7.2	7.35	7.1	7.15	44.1	Dog on table
10.33											Injection of alkali begun
11.15	175										Animal very restless
11.20	200		7.8	7.7	7.7		7.8	7.85		53.7	Injection stopped
11.30											Injection resumed, quieter
11.35	275										Deep, snorting respirations, watery defecation
11.38	355										Still defecating at intervals, profuse diuresis, pH urine, 7.85, Injection of alkali stopped
11.40			7.75	7.7	7.65	7.0	7.75	7.9	7.9	63.7	Injection of acid begun
11.41											Restless
12.16		50									Respirations 20 per minute, slow, deep and regular
12.20											
12.24		150	7.35	7.35	7.2	7.15	7.1	7.1	7.5	40.1	Respirations very slow and deep
12.38	200										
12.43	250		7.3	7.2	7.15		7.3	7.35	7.35	27.9	Dog seems in fairly good condition Still passing watery stools Recovered
1.00											

\* Injections made into leg vein, blood for examination withdrawn from jugulars, solution of bicarbonate made up in distilled water, HCl made up in 0.5 per cent salt solution. Arrows mark beginning and end of injections

2 The injection of sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) (800 c c of a  $\frac{1}{5}$  molecular solution representing 28.5 gm of the salt) into an animal of 11 kg did not produce an alkalosis or increase the buffer values, whereas the injection of 750 c c of a  $\frac{1}{15}$  molecular mixture of di-sodium phosphate ( $\text{Na}_2\text{HPO}_4$ ) and acid potassium phosphate ( $\text{KH}_2\text{PO}_4$ ) at pH 7.0 into a dog weighing 6.65 kg, produced a mild acidosis without appreciable change in buffer values.

3 The intravenous injection of 300 c c of a phosphate mixture at pH 7.4, together with 300 c c of a 4 per cent solution of sodium bicarbonate in the case of a man dying in uremic coma, caused a change in the pH of the blood from 7.35 to 7.55, and increased the buffer for alkali but not for acid. There was no change in the clinical condition of the patient, who died two hours later.

*Buffer Values in Experimental Acidosis and Alkalosis*—(Tables 10 and 11) It is seen from Experiment 1 that in the acidosis produced by the intravenous injection of an inorganic acid (hydrochloric acid) the buffer values may remain practically normal, although there is a decided lowering of the alveolar carbon dioxide and a marked increase in the pH of the blood. This is in accord with what is sometimes found in the acidosis of chronic nephritis with uremia and in that of diabetes (Table 6, Cases 4 to 9, inclusive). After injection of alkali to overcome the acidosis, there is a transient diminution in the buffer for alkali, followed by a prompt return to normal values as the pH of the blood is lowered.

In experimental alkalosis the buffer for acid is first diminished. The alveolar carbon dioxide rises to unusually high figures—63.7 mm in this animal. After injection of sufficient hydrochloric acid to overcome the alkalosis and produce a mild acidosis with lowered alveolar carbon dioxide tension, the buffer for both acid and alkali is lowered.

In the instance of mercuric chloride poisoning (Case 4, Table 4), in which the patient received large doses of sodium bicarbonate both by mouth and intravenously, a similar condition of alkalosis was produced, though here the buffer values remained normal at this stage of the disease, and the alveolar carbon dioxide tension was still low—33.0 mm of mercury.

#### SUMMARY

1 A simple method is described for determining quantitatively the buffer value of the blood. It consists in adding increasing amounts of fiftieth-normal hydrochloric acid and fiftieth-normal sodium hydroxide solution to equal quantities of blood and observing the resulting changes in hydrogen-ion concentration by means of the dialysis-indicator method.

2 The results are expressed in terms of cubic centimeters of fiftieth normal acid or alkali per 2 c c of blood

3 The buffer values of blood for acid and alkali yield valuable information from a clinical standpoint. The reserve and total buffers may also be calculated from the results of the determinations.

4 The minimal values for normal blood have been determined, considerably larger values may be encountered. For a group of miscellaneous cases with normal pH, the average buffer values were somewhat lower, though within normal limits.

5 In certain cases with normal pH of the blood, but showing a tendency toward the development of an acidosis (as evidenced, for example, by lowered alveolar carbon dioxide tension), the buffer values were diminished. The loss of buffer for alkali was far more striking and frequent than for acid, and was often associated with lowered alveolar carbon dioxide tension. As a result of therapy, especially the use of alkali, the buffer values in some instances returned to normal.

6 In a series of cases of acidosis the average buffer values were found to be markedly diminished, particularly during the stage in which the pH of the blood was abnormally high. Normal buffer values may be encountered, however, in the presence of a true acidosis. Coincident with clinical improvement following treatment, particularly intensive alkali therapy, both pH and buffer values approximated or became normal in several cases.

7 It was not possible to supply buffer to the blood by the injection of phosphate mixtures.

8 By the intravenous injection of third-normal hydrochloric acid and 4 per cent sodium bicarbonate solution into dogs, conditions of acidosis and alkalosis were produced which were inconstantly accompanied by changes in the buffer values of the blood.

9 The determination of the buffer value of the blood, especially in cases in which an acidosis is suspected or present, yields information of some diagnostic and prognostic significance and permits of a more complete study of the factors concerned in the maintenance of the acid-base equilibrium of the body.

# AN ADAPTATION OF THE ERLANGER CAPSULE TO ANY POLYGRAPH FOR OBTAINING ARTERIAL PULSE RECORDS<sup>\*</sup>

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It is now generally recognized that to understand properly the action of the heart it is necessary to employ mechanical instruments which register for comparison the simultaneous events in its various chambers

For the recording of events in the cardiac cycle two types of instruments have been devised one, for recording the ventricular contraction, depends on the application to the artery at the wrist of a metal piece or knob of a tambour, the other depends on the application of a rubber cuff or armlet encircling the arm, attached to which is a hollow rubber ball of sufficient resilience to transmit the variations of pressure to the air within a surrounding glass sphere connected with a writing tambour By this latter method, and a careful regulation of the pressure within the closed system so that it shall be maintained at a constant level between the diastolic and systolic pressure, a graphic record can be obtained, not only of the heart rate and rhythm, but also, within limits, of the variations of the intra-arterial pressure This method becomes particularly valuable when clear, accurate records are desired of the pulse in conditions associated with pulsus alternans, or the vasomotor variations of pressure occurring with periodic breathing of the Cheyne-Stokes type

Of the instruments using this closed air pressure system, that devised by Erlanger<sup>1</sup> record the variations with least instrumental variation The smoked paper attachment of this apparatus, however, renders the whole so bulky, and adds so many difficulties, that few clinicians attempt to use it at the bedside

The instruments depending for the recording impulse on the application to the artery of a metal lever or knob, require so much time to make the application and adjustment, and are so easily thrown out of adjustment, that a great share of the patience and attention of the operator is consumed in this adjustment Often the conformation of the wrist of the patient is such that no record can be obtained in this way These instruments are, for the most part, small, compact and

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<sup>1</sup> Erlanger, Joseph A Criticism of the Uskoff Sphygmotonograph, THE ARCHIVES INT MED, 1912, ix, 22

fairly accurate. Thus, while one type of instrument has the advantage of small size and portability, the other has the advantage of ease and celerity in obtaining the arterial record.

There is, therefore, a place for a device which can be readily applied, which will remain adjusted with the least attention, which will record variations of intra-arterial pressure, and which can be employed with every other form of graphic machine. These advantages seem to be obtained in the capsule of the Erlanger instrument, and I have had made by Messrs. Schneider & Brothers, who made that instrument, a bulb modified as shown in the illustration. To obtain



Figure showing an adaptation of the Erlanger capsule for use with any polygraph to record the arterial pulse. The details are explained in the text.

records, the recording tambour of any polygraph is connected with the glass bulb at A by a tube in which there may be an equalizing valve. The tube B is connected with a leather covered armlet while the tube C can be connected with any sphygmomanometer. The small inlet tube D, with the three-way stopcock is used to control the supply of air to the closed system, which consists of rubber capsule in the glass-chamber, armlet and sphygmomanometer. The stopcock is so arranged that by turning it as indicated to 'on' 'off' 'out,' the air can be pumped with an ordinary atomizer bulb into the tubes when the valve

is set at "on," and retained by turning the valve to "off," but allowed to escape by turning the key to "out" In the illustration, the protecting caps are shown screwed on the ends of the straight tube, but of course they must be removed to slip on the tubes connecting with the cuff and sphygmomanometer The sphygmomanometer is necessary to learn the systolic and diastolic pressure, so that the pressure in the recording system may be maintained at a constant point when recording, and that the changes in arterial pressure may be registered These changes occur most frequently in patients with Cheyne-Stokes type of breathing and with pulsus alternans The instrument renders it easy to apply to an artery and retain in adjustment all polygraphs, makes it possible to take records with known pressure, and to obtain records showing maximum variations due to pulsus alternans and vasomotor changes

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# A STUDY OF THE BLOOD IN HEMOPHILIA

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## INTRODUCTION

During the past few years the etiology of the hemorrhagic diseases has been the subject of considerable study. The progress made in this direction has been due largely to an increase in our knowledge of the physiology of blood coagulation and to the development of new methods of study. The literature of this period, indeed, has even given promise of an etiologic classification of hemorrhagic disease, but to the present time this goal has only been partly attained.

It has been possible, for instance, to demonstrate that certain of the hemorrhagic conditions are associated with a deficiency in one or another factor of coagulation: there are on record instances of hemorrhagic disease associated with abnormalities in the prothrombin and antithrombin content of the blood<sup>1</sup>. There is also experimental evidence of the existence of certain types of hepatic disease with some tendency to abnormal bleeding due to a deficiency in fibrinogen<sup>2</sup>. But on the other hand there are a number of clinical conditions characterized by a tendency to bleed, which at the present time cannot be rigidly classified on the basis of a defect in the fibrin factors.

Certain forms of purpura, for instance, are attributed by most workers to a deficiency in the number of blood platelets. Studies on the factors of coagulation in this disease have for the most part yielded negative results<sup>3</sup>. But repeated examinations of the blood of two patients with chronic purpura made over a period of six months have

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From the George Williams Hooper Foundation for Medical Research and the Pediatric Clinic, The University of California Medical School.

1 Whipple, G. H. Hemorrhagic Disease—Antithrombin and Prothrombin Factors. *THE ARCHIVES INT. MED.*, 1913, *xiii*, 637. Howell, W. H. The Condition of the Blood in Hemophilia, Thrombosis and Purpura, *THE ARCHIVES INT. MED.*, 1914, *xiii*, 76. Drinker, C. K. and Hurwitz, S. H. The Factors of Coagulation in Primary Pernicious Anemia. *THE ARCHIVES INT. MED.*, 1915, *xv*, 733. Following the completion of the present paper, there appeared an extensive study by Minot, Dennis and Davis (*THE ARCHIVES INT. MED.*, 1916, *xvi*, 101) on the prothrombin and antithrombin factors in a large number of varied clinical conditions. Their observation that some types of purpura may show a high antithrombin content coincides with our experience.

2 Whipple, G. H. Hemorrhagic Disease—Septicemia, Melena, Necropsy and Hepatic Cirrhosis. *THE ARCHIVES INT. MED.*, 1912, *xii*, 365.

3 Howell, W. H. The Condition of the Blood in Hemophilia, Thrombosis and Purpura. *THE ARCHIVES INT. MED.*, 1914, *xiii*, 76. See also last paragraph of Note 1.



convinced us that certain chronic types of the disease may at times show blood abnormalities in addition to a platelet deficiency. Thus, in the patients studied by us, fluctuations were observed at different times in the amount of circulating antithrombin. Periods of antithrombin excess occurred in waves during the course of the observations, but it could not be demonstrated that the increase in the amount of antithrombin was associated in any definite way with an aggravation in the severity of the clinical symptoms. These few observations are only suggestive, and from them alone no generalizations are permitted concerning the part played by the factors of coagulation in this type of hemorrhagic disease. It is not unlikely, however, that further studies may disclose other cases with a similar defect.

On the other hand, recent work has shown that the cause of hemophilia may be ascribed with considerable certainty to an abnormality in one of the factors of coagulation, and that the hemophilic condition is characterized by certain reactions of the blood which distinguish it from other hemorrhagic diseases. It is the purpose of this paper to present confirmatory evidence in support of this view.

#### VIEWS CONCERNING THE CAUSE OF HEMOPHILIA

The nature of the explanations offered for the causation of hemophilia varies with the theory of coagulation adopted. If we accept the theory of Howell, there are five factors concerned in the clotting of blood—prothrombin, antithrombin, thromboplastin, fibrinogen and calcium. All of these elements, except thromboplastin, are present in circulating blood. Within the blood vessels prothrombin is held in combination with antithrombin and intravascular clotting is thereby prevented. When, however, blood is shed, the antithrombin is neutralized by the thromboplastic substance of the tissue juices. The liberated prothrombin is now activated by the calcium and the thrombin which results converts soluble fibrinogen into the insoluble fibrin or the clot.

According to the opposing view of Morawitz, only four possible factors need be considered. The essential feature of this theory centers about the activation of thrombin, which, it is contended, results from prothrombin by the combined activity of calcium and a substance designated as thrombokinas. The existence of antithrombin in the circulating blood is admitted by Morawitz, but it is not regarded by him as an essential part of the process.

The main distinguishing feature of the hemophilic condition is the greatly prolonged coagulation time of the blood when it is removed from the vessels with the precautions necessary to prevent its contamination with tissue juices. All recent workers are agreed that this defect in coagulation is a constant pathological sign of the disease, but different explanations have been given by different workers to account

for the delayed coagulability. Hemophilia has been ascribed, indeed to a deficiency in one or another of the various elements which take part in the clotting of normal blood. Without entering into a discussion of the experimental evidence given by each observer, it may be well to review briefly the essential fact of the various views presented.

Wright<sup>4</sup> has attributed the hemophilic condition to a deficiency of calcium. Weil<sup>5</sup> has given some experimental evidence for the view that the delayed coagulability of hemophilic blood may be caused by the presence of an excess of some coagulation inhibiting body. Sahl<sup>6</sup> and Morawitz and Lossen,<sup>7</sup> adopting the theory of coagulation proposed by Morawitz, have upheld the view that the essential defect in hemophilic blood may be ascribed to insufficient or defective formation of thrombokinase. This view is shared for the most part by Nolf,<sup>8</sup> who believes hemophilic blood to be deficient in the substance designated by him as thrombozym (thrombokinase, thromboplastic substance). Aldis,<sup>9</sup> however, has given experimental proof for the view that the hemophilic condition is due to a change in the properties of the circulating prothrombin, and Howell<sup>3</sup> has concluded that not the property but the actual amount of prothrombin is altered in hemophilic blood.

During the past year we have had an opportunity to make complete blood studies in five cases of hemophilia. These patients all exhibited the hemophilic condition in marked degree, although it was not possible to obtain a definite history of hemophilia in the ascendants. A study of the blood, however, showed in each instance the characteristic delay in the coagulation time and a striking deficiency in prothrombin. From the tabulated results it will be seen that the other factors of coagulation were present in normal amounts. With one or two exceptions, the absolute amount of antithrombin present in hemophilic blood was seldom greater or less than that of normal blood, and the amount of fibrinogen was found to fluctuate little from the normal.

Our conclusions support the view that the deficiency in prothrombin is a constant characteristic of the hemophilic condition. On the basis of this observation, it is essential that a definition of hemophilia not only include the clinical characteristics of excessive and immoderate hemorrhage and its transmissibility as a sex-limited inheritance but also in addition the especial reaction of hemophilic blood which distinguishes it from the blood of other hemorrhagic diseases also characterized by a tendency to bleed.

4 Wright A E. Brit Med Jour. 1893 ii 223. *ibid* 1894, ii, 57.

5 Weil Emile P. Presse med. 1905 xiii, 673.

6 Sahl H. Ztschr f Klin Med. 1905 lii 264. Deutsch Arch f Klin Med. 1910 xcix 518.

7 Morawitz P and Lossen J. Deutsch Arch f Klin Med. 1908 xc 106.

8 Nolf P. Ergebn d inn Med, 1913 x 275.

9 Aldis T. Jour Path and Bact. 1911 x, 427.

## METHODS OF STUDY

1 *Determination of the Coagulation Time*—The coagulation time of the blood was determined according to the method employed by Morawitz and Bierich<sup>10</sup> and by Howell. A specimen was obtained by venous puncture into a syringe coated with a thin layer of petrolatum-ether mixture. Of the sample obtained, 2 c c were expelled at once into a thoroughly cleaned test tube measuring about 13 to 14 mm in internal diameter (the test tubes ordinarily used in bacteriologic laboratories serve well for this purpose). Tubes of the same diameter were used for all comparable determinations. The observations were made at a constant temperature (about 25 C). Complete invertibility of the clot was taken as the end point of the reaction. In each instance comparison was made with a specimen of blood taken from a normal individual with the same precautions. By this method the average clotting time of normal blood obtained in twenty-one tests was twenty minutes with a minimum of eight minutes and a maximum of thirty-three minutes.

It may be well to emphasize the importance of painstaking technic in obtaining blood for studies on the factors of coagulation, since a careless procedure may lead to erroneous results. In studies on the fibrin factors, interest centers on these elements as they exist in the circulating blood rather than on their behavior when blood is shed. The latter information is obtained better by a determination of the bleeding time,<sup>11</sup> the duration of which depends on a number of additional factors: the potency of the tissue juices, the mechanical and chemical action of the blood platelets, and the elasticity of the skin.

When blood is obtained by skin puncture, admixture with tissue juices invariably results. These exert an influence the extent of which cannot be measured, for it is obviously difficult to make certain that control specimens will be exposed to the same wound surface, and receive the same amount of contamination with thromboplastic substance. This point is well illustrated by an observation on the blood of one of Howell's<sup>3</sup> patients: the coagulation time of 2 c c of blood with which, owing to defective technic, some tissue juice was mixed, was 10 minutes, whereas the same amount of blood obtained at the same time directly from a vein had a coagulation time between four and five hours.

2 *Retraction of the Clot and Enumeration of Blood Platelets*—It is well known that normally a blood clot quickly retracts from the

10 Morawitz, P., and Bierich, R. *Arch f exper Path u Pharmacol*, 1907, lvi, 115.

11 According to Duke (*Jour Am Med Assn*, 1910, lv, 1185) the bleeding time is the tendency to bleed from a fresh cut. The duration of such a hemorrhage is determined by blotting up on filter paper all the blood which flows from a small incision at intervals of thirty seconds. Each drop will give, in a rough way, the volume of blood shed in the given time interval.

sides of the vessel in which it is contained and expresses serum. This phenomenon has been ascribed to the presence of the blood platelets. A deficiency in the number of these elements and nonretractility of the clot has been found to be a constant characteristic of some hemorrhagic conditions, notably purpura hemorrhagica. In both of these respects, most observers have reported hemophilic blood to be perfectly normal, but since observations on the character of clot retraction may be made during a determination of the coagulation time, and since the enumeration of blood platelets is not difficult, a record of both of these factors should be made, if possible, in all complete studies of the blood in hemorrhagic conditions.

The presence or absence of clot retraction is determined simply by incubating the clot at 37.5 C. for from twelve to twenty-four hours. In normal blood retraction begins after several hours, and is complete within eighteen to twenty-four hours; in pathologic blood, on the contrary, contraction may occur only after a long time or not at all.

For the enumeration of blood platelets a number of methods are available, but that of Wright and Kinnicutt<sup>12</sup> appears to have given the most reliable results in the hands of most workers. It has been our experience that successful counts can be obtained only with freshly prepared solutions and with perfectly clean apparatus.

3 *Quantitation of the Fibrin Factors—Method of Notation*—The recorded observations include only determinations of prothrombin, antithrombin and fibrinogen. There is little of positive evidence in favor of the view that a deficiency of calcium exists in hemophilic blood (Morawitz and Lossen,<sup>7</sup> Nolf,<sup>8</sup> Addis,<sup>9</sup> and Hess<sup>13</sup>). A consideration of this factor, therefore, may be omitted in this study. According to the best experimental proof the existence of a thrombokinase in the sense of Morawitz is hypothetical. What is usually designated as thrombokinase in the blood and other tissues is the coagulation accelerating substance known under the terms of zymoplastic (Schmidt) or thromboplastic substance (Nolf and Howell). Whether or not this material is deficient in hemophilic plasma cannot be determined with any certainty because no direct method of studying this factor is available. Some information concerning this substance as it exists in the blood can be obtained by an enumeration of the platelets, for these elements as will be recalled are an important source of thromboplastic substance. But information obtained from this source is incomplete inasmuch as all of the formed elements of the blood have been shown to possess thromboplastic properties to a greater or less extent.

12 Wright I. H. and Kinnicutt R. A New Method of Counting the Blood Platelets Jour. Am. Med. Assn., 1911, lv, 1457.

13 Hess A. F. Bull. Johns Hopkins Hosp., 1915, xxxi, 372.

*Prothrombin and Antithrombin*—The methods developed by Howell for the determination of prothrombin and antithrombin have been reviewed extensively in recent literature (Howell,<sup>3</sup> Drinker and Hurwitz<sup>14</sup>), and only brief reference to them will be made in this paper. The prothrombin deficiency which forms such a distinguishing feature of hemophilic blood, in contrast with other bloods, is demonstrated very clearly if to the specimen of clear plasma obtained by first oxalating and centrifugalizing the blood, calcium chlorid is added in optimum concentration. A specimen of normal blood so treated shows usually a coagulation time as measured by the invertibility of the clot of about ten minutes, whereas, the clotting time of hemophilic blood, treated in a similar manner, may be delayed from one to four or five hours.

Protocol 1 gives the results of one of the comparisons made between hemophilic and normal blood (Table 1), and shows the manner in which the reaction is carried out in practice.

PROTOCOL 1—PROTHROMBIN TEST (CASE 3, Nov 1, 1915)

Oxalated Plasma, Drops	CaCl <sub>2</sub> 0.5 Per Cent, Drops	Coagulation Time	
		Patient	Control
5	1	Clot in 24 hours	14 minutes
5	2	Partly clotted in 3 hours	12 minutes
5	3	Clot in 180 minutes	14 minutes
5	4	Partly clotted in 3 hours	14 minutes

The control specimen of blood in this particular experiment, it will be noted, clotted in twelve minutes. In order to indicate the extent of the delay in coagulation shown by the recalcified plasma, the term prothrombin quotient has been introduced. This is obtained by dividing the coagulation time of the specimen of pathologic plasma containing the optimum amount of calcium by the coagulation time of the normal blood tested at the same time and by the same method. In the present instance the prothrombin quotient is 180 divided by 12 or 15. This indicates in a rough way that in this particular experiment the coagulation time of hemophilic blood was fifteen times that of normal blood. In subsequent paragraphs it will be shown that this figure, however, has no especial clinical significance inasmuch as the gravity of the hemophilic condition has not been found proportional to the length of time required for the plasma to clot.

<sup>14</sup> Drinker, C. K., and Hurwitz, S. H. The Factors of Coagulation in Primary Pernicious Anemia, *THE ARCHIVES INT. MED.*, 1915, *v*, 733.

The method of determining the amount of antithrombin in hemophilic and in normal blood may likewise be rendered clearer by a specific example (Protocol 2)

PROTOCOL 2—ANTITHROMBIN TEST<sup>15</sup>

Heated Plasma, Drops	Thrombin, Drops	Time Interval, Minutes	Fibrinogen, Drops	Coagulation Time, Minutes	
				Patient	Control
1	2	15	7	23	19
1	3	15	7	15	13
1	4	15	7	11	12
1	5	15	7	8	8
				57	52

$$\text{ANTITHROMBIN QUOTIENT} = 57/52 = 1.1$$

The use of the term antithrombin factor was suggested by Denny and Minot<sup>17</sup> to make the results obtained at different times and with different reagents comparable, but the term antithrombin quotient appears to us to be more appropriate. This quotient is obtained as shown above by dividing the average of a series of suitable determinations of the pathological blood by a similar figure obtained for a control specimen. It is obvious that if the antithrombin content of the patient's blood and that of a control are the same, the antithrombin quotient will be about unity. Slight fluctuations above or below one are within the experimental error and may be regarded as normal.

*Fibrinogen*—Determinations of fibrinogen were made by the heat coagulation method described in a previous communication.<sup>17</sup> We are aware that this method of estimating fibrinogen is not beyond criticism, and that even normal individuals may show considerable variation in the amounts of fibrinogen determined in this way. In man, however, these fluctuations are not so great as in healthy animals. For clinical studies, therefore, this method is sufficiently accurate, especially if it be kept in mind that variations in the amounts of fibrinogen in disease in order to be of real significance should be of considerable magnitude.

4 *Quantitation of Serum Proteins*—The availability of a simple and accurate method made possible a study of the different serum proteins in each of the five patients under observation. For this purpose the microrefractometric method recently described by Robertson<sup>18</sup> was

15 The solutions of thrombin and fibrinogen necessary for carrying out the test were prepared according to Howell's method (Howell W. H., *Am. Jour. Physiol.*, 1913, xxxii, 264).

16 Denny, G. P. and Minot, G. R., *Am. Jour. Physiol.*, 1915, xlii, 227.

17 Whipple, G. H. and Hurwitz, S. H., *Jour. Exper. Med.*, 1911, xxi, 177.

18 Robertson, T. B., *Jour. Biol. Chem.*, 1915, xxxi, 235.

found very useful. The hemophilic blood is allowed to clot spontaneously or else coagulation is hastened by shaking with glass beads, and determinations are then made of the serum albumin, serum globulin, and total protein. The purpose of such a study would be to detect the presence of any abnormality in the protein partition products, should any arise during the clotting of pathological blood. So far as the authors are aware, this phase of the study of hemophilic blood has received no attention from previous workers.

5 *Fibrinolysis*—The possible occurrence of fibrinolytic ferments in the blood of patients exhibiting hemorrhagic tendencies has been entertained by several observers. Such ferments have been demonstrated in some intoxications in animals and in man in certain types of leukemia and in hepatic insufficiency.<sup>19</sup> Morawitz and Lossen,<sup>7</sup> who studied this point in hemophilia, found no indication of fibrinolytic activity.

The test is easily carried out, and we believe should be done as a routine on every specimen of pathological blood examined. It is simply necessary to incubate the clot at body temperature, and to observe whether any dissolution occurs in the stated time interval. Since the clot from any specimen of blood will undergo a certain amount of dissolution if left in its serum a sufficient length of time, it is well to restrict the term pathological fibrinolysis to instances of complete clot dissolution occurring within twelve hours when the blood is kept at body temperature.

#### CLINICAL RECORDS AND BLOOD EXAMINATIONS

In a thorough analytical study of the hereditary aspects of hemophilia, Bulloch and Fildes<sup>20</sup> conclude that instances of probable hemophilia without demonstrated inheritance are comparatively few. It is their opinion that the introduction of the "de novo" concept is based on the inability of authors to demonstrate the line of inheritance in their cases. When it is remembered, however, that the other bleeders necessary to establish the inheritance of the condition may not be members of the same family, but of collateral branches, it is clear that the hereditary characteristics can be proved only with great difficulty.

It is fair to state that cases arising spontaneously or "de novo" without a history of bleeding in the family, have been recorded,<sup>21</sup> and

19 Goodpasture, E. W. Bull. Johns Hopkins Hosp., 1914, XXV, 330.

20 Bulloch, W., and Fildes, P. Eugenic Lab. Memoirs, Univ. of London, 1911, 169.

21 Wright reports four cases without a hemophilic ancestry (Ref. 23, p. 926). Bulloch and Fildes give at length the history of a hemophilic family studied by Gettings, who was unable to find any instances of the disease among the collaterals, although these were widely inquired into over a number of generations (Ref. 20, pp. 191 and 343). In four of Schloessmann's (See Ref. 29) seven patients no history of heredity could be demonstrated, and this was true of one of Howell's patients.

that perhaps too much stress has been laid on the hereditary features. In the patients observed by us no definite history of hereditary transmission could be obtained, notwithstanding care in questioning although it is not unlikely that the bleeding tendency existed somewhere in the direct ascendants or in the collateral branches of these families. But it is not justifiable to exclude such cases from the group of hemophilia, because there is no evidence of a similar condition in the family records. As has been shown by Howell, hemophilia is characterized by certain properties of the blood which distinguish it from other hemorrhagic diatheses. These, we believe, furnish a convenient method of making a diagnosis of hemophilia even in the absence of any proved history of the existence of the disease in the patient's antecedents.

CASE 1—*Clinical History*—(Hospital No 6305) George R, aged 6 years American born, of Swedish parents, was admitted to the University of California Hospital first in October, 1913, complaining of profuse and frequent nosebleed. Since then the patient has received treatment in this hospital at four different times (Hospital Nos 6867, 8035, 9355, and 9572), each time for excessive hemorrhages associated with his hemophilic condition.

The patient's father was living and well, his mother was a healthy woman 44 years of age. According to her account she had had frequent attacks of epistaxis, and when 24 years of age had a profuse hemorrhage following the extraction of a tooth. She had noted that "black and blue" spots appeared occasionally on different parts of her body following slight trauma. Concerning the patient's ascendants, no definite information could be obtained, nothing was known of the paternal or maternal grandparents. The patient's aunt had four or five boys who were apparently free of any hemophilic taint. The patient had one sister 9 years of age who was in perfect health, and had at no time shown any signs of a hemophilic tendency, and, according to studies of her blood there was no abnormality existing at the present time (M R, Table 3). Two children had died when a few days old. The cause of their death was not known to the mother.

The patient was a full-term child, his development had been normal. The most important feature of his past history was an attack of pertussis at the age of  $2\frac{1}{2}$  years. The frequent hemorrhages from the nose, which form such a persistent symptom of his present condition, dated from this infection. In September, 1913, several weeks previous to his first admission for epistaxis, the patient cut his hand and bled for four days. Bleeding from the nose continued at intervals during his first four months' stay in the hospital. At times the hemorrhages were very severe and various forms of treatment were tried: two direct transfusions with little immediate or permanent effect on his condition, and the injection of human and rabbit's blood serum and of rabbit's whole blood both subcutaneously and locally to the bleeding points.

The patient was again admitted for profuse epistaxis twenty-two days following his discharge from the hospital. Two days after entrance he had a profuse hemorrhage from the stomach and for the next few days passed tarry stools. So far as could be learned, this was the first sign of the gastro-intestinal hemorrhages which had occurred also during his last admission to the hospital. The treatment this time consisted simply of local application of horse serum to the nasal mucosa. After a four months' stay (January to May, 1914) the patient again returned in October, 1914 because of bleeding from a wound in the arm. In June, 1915 the occurrence of epistaxis and vomiting of blood necessitated the patient's re-admission to the hospital. The gastro-intestinal hemorrhages which had appeared first in January, 1914, had now recurred.



*Examination and Clinical Course*—The positive physical findings were essentially the same during each admission extreme yellow pigmentation of the skin, sclerae, and mucosae, a loud blowing systolic murmur and a palpable liver and spleen During his first admission, a few small petechial hemorrhages were noted over the skin of the chest, abdomen and thigh, and during his last admission a note was made of small purpuric areas over both legs and of a similar area of large size about the left elbow

This time the patient remained in the hospital about three months On the first and second days following his admission, he received two subcutaneous injections of his father's blood, one of 6 cc and one of 20 cc Bleeding from the nose subsided, and the hemoglobin rose gradually from 15 to 40 per cent (Dare) For a period of seventeen days (June 14 to June 30) the patient was fed on 0.1 gm of kephalin daily<sup>22</sup> This was supplemented by three subcutaneous injections of 0.05 gm of kephalin These injections caused a rise in temperature, and small areas of redness, infiltration, and local tenderness From August 1 to 25 kephalin in doses of 0.1 gm was again administered by mouth This therapy was continued with the hope of modifying the coagulability of the blood, although the patient, at the time the treatment was undertaken, had no severe attacks of bleeding

#### CLINICAL SUMMARY AND BLOOD EXAMINATIONS

Certain points in the history of this patient deserve special mention first, the absence of a definite history of bleeding in the family, second, the appearance of the first signs of uncontrollable hemorrhage at the age of 2½ years following an attack of whooping cough, and their persistence with intermissions for a period of five years In this connection it is of interest that the hemorrhages had been confined with few exceptions to the nasal mucosa, and that trauma had been a factor in their causation only twice, third, the absence of hemarthroses and articular effusions This is in striking contrast to the clinical histories of Cases 2 and 3, which will be discussed later

At different times during the patient's stay in the hospital and for a period following his discharge from the hospital, studies were made of the factors of coagulation and of the formed elements For purposes of brevity, the separate protocols have been omitted and the results presented in Table 1 The first observations on the blood coagulability were made June 11, five days after a persistent nasal hemorrhage The coagulation time was found markedly delayed, 335 minutes as compared with thirty-two minutes for a normal control Five days previously the patient had received several small injections of whole blood, which apparently had not influenced his condition The prothrombin, as will be noted from the table, showed the deficiency characteristic of this disease, the coagulation time of the recalcified plasma being about nine times as great as the control Antithrombin was present in very slight excess A second observation made September 2 following an interhemorrhagic period of two months, showed the same marked delay in coagulation, although to a less extent, but, as

<sup>22</sup> The kephalin used in these studies was prepared according to the method outlined by Howell (Am Jour Physiol, 1912-1913, xxxi, 1)

will be noted, the deficiency in prothrombin was found to be actually more marked. This observation illustrates clearly that the extent of the delay in coagulation is demonstrated with greater accuracy if the blood is first oxalated and then recalcified. The antithrombin at this time was present in normal amount, and remained uninfluenced by the administration of kephalin during the months of July and August.

Six weeks after the patient's discharge from the hospital another examination of the blood was made (October 18). This observation is of extreme interest, because the blood obtained with the usual precautions and without admixture with tissue juices showed a more rapid coagulation time and a less striking prothrombin deficiency. Antithrombin was present in normal amount and the fibrinogen was slightly increased. It is difficult to explain this great increase in the coagulability of the blood. A similar improvement was noted also in Case 5, to which reference will be made later. It would appear that coincident with the waves of improvement observed clinically in these patients, there may also be some alteration in the coagulability of the blood. This improvement, however, was temporary, for two final observations, one on November 10 and another December 15, exhibited the same delay in coagulation and the same prothrombin deficiency as were recorded in June. The prothrombin observations in this patient showed that this factor is diminished in the interhemorrhagic interval as well as during the period of active hemorrhage. The observations indicate, however, that this deficiency in prothrombin may be less striking immediately following a period of profuse bleeding.

From the tabulated results, it is apparent that the retractility of the blood in this instance was normal. This is well in keeping with the persistence of a normal platelet count throughout the period of observation. These elements had been followed in this patient for over a year (Table 4) but, with two exceptions, they had been found normal or above normal. The table contains also observations on the number of white corpuscles and the relative percentage of each found in over twenty-five counts. It will be seen that the average number of leukocytes in this series was 2,150 and that of these 53 per cent were polymorphonuclear elements. This is in harmony with the observations of Wright<sup>23</sup> and of Sahli,<sup>24</sup> both of whom found a subnormal number of leukocytes and a smaller percentage of polymorphonuclear cells in hemophilic blood.

No fibrinolytic activity was noted in the blood of this patient and an analysis of the serum expressed from the clot after its slow formation showed a normal percentage of serum albumin and of serum globulin.

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<sup>23</sup> Wright, A. F. *Albert's System of Medicine*. 1922, 1935.

CASE 2—*Clinical History*—(Hospital Nos 10055 and 10343). James McC aged 6 years, was admitted to the University of California Hospital, October, 1915. Three days before admission the patient fell and struck his left eye. The wound thus received was still bleeding on admission.

Although the parents were carefully questioned, no history of any hemophilic tendency in the immediate ascendants could be obtained. The paternal grandfather was 78 years old and in good health, the paternal grandmother died of cancer at the age of 48 years. The maternal grandmother was 71 years

TABLE 1—SUMMARY OF BLOOD

Case	Date	Hydrogen Ion Cone P H*	Coagulation Time, Minutes		Retrac- tility of Clot	Fibrino- lysis	Platelets (Thrombo- plastin)
			Patient	Control			
Case 1, G R	6/11		335	32	+	0	352,000
	9/12	7.6	195	15	+	0	
	10/18		23	16	++	0	
	11/10	7.75	240	19	+	0	
	12/15		220	30	—	0	
Case 2, J McC	10/ 8		49	16	—	0	580,000 (Oct 12)
	10/18	7.65	240	19	+-	0	
	10/21				—		192,000
	10/28		180	30	—	0	
	11/ 5	7.7	120	20	—	0	
	12/ 3		180	15	+	0	
	12/ 8		170	15	—	0	
	12/15		138	30	+	0	
	12/20		210	20	+	0	
Case 3, D McC	10/11		225	20	+	0	160,000
	11/ 1	7.75	240	18	+	0	
	12/ 3		180	15	+	0	
	12/ 8		240	15	+	0	
	12/15	7.7	145	30	+	0	
	12/20		240	20	+	0	

\* The reaction of the blood was determined colorimetrically by the method proposed by Levy, Rowntree and Marriott (*THE ARCHIVES INT MED*, 1915, vi, 389)

of age, she had two brothers and five sisters, who were well. So far as could be learned, the sister's children were well, none having been troubled with bleeding. The patient's mother was of a family of two brothers and three sisters. The brothers were well. The one sister had two boys, both of whom were well.

The hemophilic tendency was first noted by the mother when the child was 3 months old. At that time she had noticed the appearance of "black and blue" swellings over the soles of the feet and the backs of the elbows following the slightest trauma. When 2 months old the child fell and struck his head. A large hematoma formed, which was opened. Bleeding from the wound continued for about two months and left the child extremely exsanguinated. At the age of 17 months the patient nicked his gum by the upper central

incisors and bled for a period of two weeks. At 2½ years of age, and again when 4 years of age, severe attacks of bleeding followed injuries above the right eye.

Joint effusions occurred repeatedly, the slightest trauma to an exposed joint having been followed by a painful swelling with areas of discoloration. The knees had suffered more than any other joints, and as a result of the repeated attacks these joints had become somewhat deformed, and showed considerable limitation of motion.

#### EXAMINATIONS IN CASES 1, 2 AND 3

Prothrombin			Antithrombin			Fibrinogen In Gm per 100 c c	Treatment
Patient	Control	Quotient	Patient	Control	Quotient		
76	8	9.5	14	40	1.1	0.494	Ten cubic centimeters whole blood given subcutaneously June 5, and 20 c c June 6. Kephallin 5 c c (0.05 gm) subcutaneously on July 1, 4 and 7. Elevation of temperature to 10 C and local reaction. Kephallin 0.1 gm doses daily from August 1 to August 25.
180+	7	25 +	36	40	0.9		
57	10	5.7	40	47	0.8		
160	17	9.4	61	82	0.8	0.120	October 7 and 8 wound packed with sterile cotton soaked in 2.5 per cent sterile kephallin and firm pressure applied. Twelve intramuscular injections of 5 c c kephallin (2.5 per cent sterile solution) from October 7 to 15, and 9 intramuscular injections of 5 c c kephallin (1 per cent in 6 per cent glucose solution) from October 16 to 27. December 1 to 4 and 8 to 11 inclusive exposure of tibiae and femora to Roentgen rays. Dose 5 milliamperes minutes.
60	11	4.3	26	20	1.4		
195	10	19	37	47	0.8		
90	19	4.7	63	67	0.9	0.366	December 1 to 4 and 8 to 11 inclusive, exposure of tibiae and femora to Roentgen rays. Dose 5 milliamperes minutes. Discontinued after this time because of low platelet count and prolongation of bleeding time.
60	10	6.0					
85	15	5.6	91	38	2.3		
72	25	2.8	103	103	1.0	0.250	December 1 to 4 and 8 to 11 inclusive, exposure of tibiae and femora to Roentgen rays. Dose 5 milliamperes minutes. Discontinued after this time because of low platelet count and prolongation of bleeding time.
115	17	6.7	50	99	0.5		
200	11	14	130	149	0.9		
150—	12	12 —	44	32	1.3	0.250	December 1 to 4 and 8 to 11 inclusive, exposure of tibiae and femora to Roentgen rays. Dose 5 milliamperes minutes. Discontinued after this time because of low platelet count and prolongation of bleeding time.
180	12	15	77	52	1.1		
85	15	5.6	92	38	2.3		
95	25	3.8				0.250	December 1 to 4 and 8 to 11 inclusive, exposure of tibiae and femora to Roentgen rays. Dose 5 milliamperes minutes. Discontinued after this time because of low platelet count and prolongation of bleeding time.
127	17	7.1	116	119	1.0		
180	14	12	128	149	0.9		

*Examination and Clinical Course.*—Apart from the condition in the knee joints the local injury was the chief feature in the physical examination. The left eye was swollen and completely closed, a large area of ecchymosis extended over both eyelids and over the upper part of the left cheek. Bleeding came from the small incised wound which however was found to be quite deep.

Soon after admission the wound was cleaned and packed with gauze saturated in a 2½ per cent solution of kephallin which had been freshly prepared and sterilized. Some of the kephallin mixed with sterile vaseline was made into a paste and also pressed into the wound. This was repeated several times and even after firm pressure was applied the oozing of blood still continued. The patient was given 500 mg of vitamin K and 100 mg of ascorbic acid daily. The patient was given 500 mg of vitamin K and 100 mg of ascorbic acid daily.

five days, however, the swelling and ecchymosis had commenced to disappear. On the sixth day, the pack was removed from the wound without the occurrence of any bleeding. As indicated in Table 1, the local application of kephalin was supplemented by intramuscular injections—twelve injections of 5 c.c. each of a 2½ per cent solution of kephalin in water were given from October 7 to October 15, and nine such injections of a 1 per cent solution in 6 per cent dextrose, from October 16 to October 27. Notwithstanding the frequent repetition of these injections, no local induration or tenderness appeared, nor did the patient show any untoward constitutional symptoms.

Three weeks after admission a slight trauma of the right ankle caused a hemarthrosis which subsided within a week, but for which the patient was readmitted several weeks later. During this second admission, the effects of suberythema doses of Roentgen ray<sup>24</sup> on the factors of coagulation was tried. Exposure of the long bones was made daily from December 1 to 4 and from December 8 to 11 with an intermission of four days. The principles underlying this mode of treatment and its value in this disease will be discussed in subsequent paragraphs.

**CASE 3—Clinical History**—(Hospital No 10345) Daniel McC, aged 9 years, brother of James McC, was admitted in November, 1915, complaining of swelling and pain in the left knee joint.

Both brothers gave strikingly similar histories, in the younger of the two, the symptoms of the disease had also appeared early in infancy. The mother stated that when the child was 3 months old, she had noticed for the first time bluish areas of discoloration over different parts of the body subjected to the slightest injury. When 11 months old, on first attempting to walk, the child injured his right knee. This injury, although not severe, caused an effusion into the joint. From that time to the present, considerable difficulty had been experienced with bleeding from minor accidents, three very severe hemorrhages having occurred between the ages of five and seven years—two of these followed cuts over the right and left eyes, and one followed an injury to the palm of the right hand, from which oozing continued for four months. Nearly every exposed joint in the body had been the site of an effusion. At the age of 4 years a fall on the left elbow resulted in complete disability for a period of a year. When 8 years of age, another severe hemorrhage followed the loosening of an incisor tooth.

**Examination and Clinical Course**—Many ecchymotic areas of varying size were present over the arms and legs. These, together with the joint manifestations, constituted the chief findings on physical examination. All of the joints were found somewhat enlarged, but the knees were principally affected. The right knee was irregular in contour, and showed some impairment of motion. The left knee was swollen and tender. A few ecchymotic areas were present above and below the patella. Roentgenograms of the left knee showed marked distention of the synovial sac and some loss in definition of the articular surfaces. The latter presented the appearance of a chronic arthritis. Five days' rest in bed and moderate immobilization of the joint caused some absorption of the effusion and a subsidence of the pain, but the effusion returned following a repetition of the trauma, once fourteen days and again twenty-four days after admission.

In this patient also a study was made of the effect of short exposures to the Roentgen ray on the coagulability of the blood. Eight exposures of 5 milliamperes minutes each were given, the interval between each four exposures being four days. At the end of this period the exposures were stopped because the reduction in the number of platelets and the prolongation of the bleeding time made it unwise to continue the treatment.

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<sup>24</sup> Exposure made at 12 inch target skin distance with Coolidge tube, 3 mm aluminum filter, 6 inch parallel spark gap, 5 milliamperes minutes, 1/20 erythema dose. We are much indebted to Dr H. E. Ruggles of the University of California Hospital for making the exposures.

## CLINICAL SUMMARY AND BLOOD EXAMINATIONS OF CASES 2 AND 3

The clinical histories of both brothers differed in several interesting points from that of Case 1. In them the first symptom of the hemophilic condition made its appearance in early infancy. The application of trauma was for the most part the initiating cause of the hemorrhages beneath the skin, from the open wounds, and into the synovial sacs. Repeated involvement of the joints, especially the knees, was one of the most striking symptoms in both patients, and in each instance these articular lesions resulted in chronic arthritis with deformity and disability.

The blood of each of these patients showed during every examination the characteristic prothrombin deficiency. It will be noted, however, that wide fluctuations in this factor were observed from time to time. These variations may best be considered in connection with the clinical condition and the form of treatment which was carried out. The first examination of the blood in Case 2 was made four days after the onset of bleeding (October 8). As the tabulated results indicate the coagulability of the blood during this period was markedly increased. This is the only time that such a diminution in coagulation time during an attack of hemorrhage was observed in any of the patients. Increased coagulability of the blood, on the other hand, has been noted twice during the interhemorrhagic period (Cases 1 and 5). It would seem, therefore, that the contention of Sahl<sup>6</sup> that, during the hemorrhagic period hemophiliacs usually show a reduced or even a normal coagulation time, is not supported by our studies.

In other respects the blood of both brothers showed no abnormalities. Clot retraction was normal, and the percentages of the serum proteins and the plasma fibrinogen did not vary widely from values obtained for normal blood. With one exception, the antithrombin factor approximated one. In both patients a transitory antithrombin excess was observed about forty-eight hours following the commencement of exposure to the Roentgen rays. The effect of such exposures on the prothrombin-antithrombin balance will be discussed later.

**CASE 4—Clinical History.**—Arthur S., aged 13 years, came to the dental clinic of the University of California in June, 1915, complaining of toothache. Because of his unusual history of repeated attacks of uncontrollable hemorrhage, Dr. C. R. Giles kindly referred him to us for observations on the coagulability of the blood.

So far as we could learn from the patient's mother, no bleeding trouble had existed in any members of her family. She had four sisters, all of whom had boys, but none of these had a similar trouble. She herself had one boy, aged 5 years, on account of some internal hemorrhage following an accident. But it was not possible to find out the exact circumstances of this boy's case. It is of interest that this child, as a result of his accident, it was feared that the operation might result in a cure of the bleeding.

The patient showed the first signs of the hemophilic tendency in early infancy. Circumcision performed ten days after birth was attended by profuse bleeding from the wound lasting for a number of days. From that time to the present great difficulty had been experienced with bleeding from minor accidents. When 1 year old the patient bit his tongue and bled profusely for six days. A similar accident to the gums two and a half years later again resulted in a profuse hemorrhage. This was unaffected by the application of styptics and the thermocautery. The first attack of epistaxis occurred at the age of 4 years, and since then the attacks have been frequent, especially in warm weather. Three very severe hemorrhages occurred between the ages of 6 and 10 years: the first followed an injury to the hand, which bled for over a week, the second and third attacks of bleeding were occasioned by extraction of teeth. Several months ago the patient again had four teeth extracted, and bled for seven to eight days.

CASE 5—*Clinical History*—Edward O., aged 11 months, came under observation in October, 1915. The patient was seen first by Dr. Florence M. Holsclaw, to whom we are much indebted for the opportunity of studying the blood and for the clinical notes.

TABLE 2—SUMMARY OF BLOOD

Case	Date	Hydrogen Ion Conc. + P H	Coagulation Time, Minutes		Retractility of Clot	Fibrino- lysis
			Patient	Control		
Case 4, A. S.	6/21		150	23	+	0
	10/29	7.8	210	31	+	0
	11/20	7.7	150	30	+	0
Case 5, E. O.	10/26		305	30	+	0
	11/18	7.6	50	8	+	0
	12/15					
	12/20		120	20	++	0

The baby was an illegitimate child, and because of this circumstance, information concerning the family history was not obtainable. The essential facts regarding the child's health since birth and the circumstances pertaining to the present illness were obtained from Dr. Holsclaw's records. From this account it was apparent that the child had been in perfect health before the onset of the present illness. A week before the baby came under observation the nurse had noticed several "black and blue" spots, both large and small scattered over the body. It was also noted that the child was fretful, nervous and wakeful at night. Two days following the appearance of the ecchymoses on the body, similar ones were noticed over both cheeks, and a few days later (October 21) a large swelling involving the whole of the left cheek appeared. The skin over the swelling was discolored, tense, and shiny, and the veins over it were dilated. The interior of the mouth was dark purplish in color. There was also a bulging inside apparently due to an effusion of blood under the mucous membrane. Palpation of this swelling did not elicit pain and there was no elevation of temperature.

The baby was taken to Lane Hospital, October 22, where the coagulation time of the blood was tested (Addis). This was only roughly estimated since it seemed undesirable to puncture a vein or even to make a new skin puncture. Only blood oozing from a puncture in the big toe made some hours before

able. Capillary tubes were filled with this blood, and these were estimating the coagulation time. In two tubes times of seventeen and minutes were observed as compared with a normal of seven minutes; the next few days the swelling and ecchymosis of the left cheek began to disappear, and bleeding from the needle prick made in the big days previously (October 23) was at length stopped by pressure. On the 26 the child was brought to the University of California Hospital. A puncture was done for a study of the factors of coagulation. Two examinations were made subsequently, one November 18 and another on 20. At the time the patient was seen last, the swelling of the cheek had entirely disappeared, the "black and blue" spots had faded, and the general condition was excellent.

#### EXAMINATION OF THE BLOOD

The main points derived from a study of the blood of both of these cases have been presented in Table 2. In a general way the findings in these cases correspond to those recorded in Table 1, but it may be

#### CASES 4 AND 5

Prothrombin		Antithrombin			Fibrinogen in Gm per 100 c c
Control	Quotient	Patient	Control	Quotient	
9	8	14	17	0.8	0.378
16	6	43	37	1.1	0.425
12	10	31	28	1.1	0.290
10	9	50	53	1.0	
17	5	120	90	1.3	
14	14	170	149	1.1	

call attention to several features which deserve special attention.

During the period of observation, the fourth patient had no attacks of bleeding, but the blood showed, nevertheless, the characteristic delay in clotting, instability and a marked prothrombin deficiency. All of the other factors, as will be noted, were normal. The first observation in Case 4, on the other hand, was made only a few days after the onset of the disease, and while the patient was still bleeding. It will be noted that the coagulation time was markedly prolonged and the antithrombin much reduced in amount. During a subsequent examination, however, made about three weeks later, when active bleeding had ceased, great improvement was noted also in the condition of the blood, but as is characteristic of this disease, the increase in blood clotting was only temporary. For a third observation a month later the blood returned to the initial condition.



The observations on the blood platelets in this patient are of extreme interest. It will be recalled that a small skin puncture, made several days after the onset of the symptoms, bled for about three days notwithstanding the application of firm pressure. This extreme prolongation of the bleeding time is well in keeping with the low platelet count (64,000) obtained at this period. Enumeration of these elements about two months later, when all signs of acute hemorrhage had disappeared, showed them to be normal. It is justifiable to conclude, therefore, that the extreme prolongation of the bleeding time was due in this instance to a deficiency in blood platelets. None of the other patients observed showed such a marked platelet deficiency, and it would appear that its occurrence is rare in hemophilia, although reduction in the number of

TABLE 3—RESULTS OF EXAMINATION OF BLOOD OF SISTER OF CASE 1 AND OF MOTHER AND SISTERS OF CASES 2 AND 3

Case	Member of Family	Coagulation Time, Minutes		Prothrombin			Antithrombin		
		Pa-tient	Con-trol	Pa-tient	Con-trol	Quo-tient	Pa-tient	Con-trol	Quo-tient
1	Sister (M R)	23	—	9	10	0.9	17	19	0.9
2	Sister (Agnes MeC)	23	20	12	9	1.3	58	49	1.1
	Sister (Adeline MeC)	20	23	12	10	1.2	52	50	1.0
	Mother	16	19	14	10	1.4	20	25	0.8

these elements has been noted by some observers<sup>25</sup>. Of interest also is the fact that the prothrombin remained low even when the platelets had returned to a normal level. The relation of blood platelets to the origin of prothrombin will be considered in another connection.

#### DISCUSSION OF RESULTS

Apart from the special abnormality in the fibrin factors to which reference has been made, a study of the blood of our hemophilic patients showed that hemophilic and normal bloods differ in no other respect. According to our observations, a change in the activity of the fibrin factors is not due to any alteration in the reaction of the blood, for we have found the hydrogen-ion concentration of hemophilic blood serum to vary little from that of normal blood. There also is no abnormality in clot retractility, which constitutes the third phase of coagulation. In this respect hemophilia differs from some other hemorrhagic

<sup>25</sup> Austin, J. H., and Pepper, O. H. P. Experimental Observations on the Coagulation of Oxalated Plasma, with a Study of Some Cases of Purpura, *THE ARCHIVES INT. MED.*, 1913, 21, 305.

conditions, notably purpura, in which this phase of coagulation has been found abnormal. The clot in hemophilic blood is slow to form, but it possesses normal retractile power, in fact, in several instances, the retraction of the clot and the expression of serum was greater in hemophilic than in normal blood.

In still another particular, hemophilic blood has been found normal. An analysis of the serum after coagulation has shown that the percentage of serum albumin and serum globulin approximates very closely that of normal human blood. It is true, as the tabulated results show (Table 6), that the average percentage content of total proteins is somewhat diminished in hemophilic blood, and that the globulin fraction shows a slight relative excess, but these differences are too small to possess real significance. On the whole, the results indicate that no abnormality in the protein partition products arises during the clotting of hemophilic blood, and that the change observed in the fibrin factors cannot be brought into association with any alteration in the serum proteins.

As already pointed out, our observations support the view of Howell that the essential cause of the delayed coagulability of hemophilic blood is attributable to a deficiency in the circulating prothrombin. The other factors of coagulation have been followed. Gravimetric determinations of the fibrinogen content of hemophilic blood have convinced us that no abnormality exists in this element. This finding is in harmony with those of Sahli,<sup>6</sup> who weighed the fibrin produced by the coagulation of hemophilic blood, and found it to be within the limits of normal variation. That no qualitative defect in this factor exists has been shown by Addis.<sup>7</sup> By the addition of varying amounts of thrombin to fibrinogen prepared from hemophilic blood and from normal blood, he was able to demonstrate that the former clots as rapidly as the latter. It is possible to conclude from the available experimental evidence, therefore, that no qualitative or quantitative defect exists in the fibrinogen of hemophilic plasma.

According to our results, the amount of antithrombin in hemophilic blood also exhibits little variation from the normal. For the most part, the antithrombin quotient was only slightly above or below one. Such fluctuations as were observed may be considered to lie within the experimental error for the quotient seldom showed variations from one greater than several tenths. It is of interest that a definite excess of antithrombin was demonstrable in the blood of two patients about forty-eight hours after the commencement of Roentgen-ray exposures (Cases 2 and 3). This rise however was only transitory and was no longer present five days later. These results do not support the view held by some observers that the delayed coagulability of hemophilic blood is due to an absolute excess of antithrombin,<sup>8</sup> nor are they in harmony

The observations on the blood platelets in this patient are of extreme interest. It will be recalled that a small skin puncture, made several days after the onset of the symptoms, bled for about three days notwithstanding the application of firm pressure. This extreme prolongation of the bleeding time is well in keeping with the low platelet count (64,000) obtained at this period. Enumeration of these elements about two months later, when all signs of acute hemorrhage had disappeared, showed them to be normal. It is justifiable to conclude, therefore, that the extreme prolongation of the bleeding time was due in this instance to a deficiency in blood platelets. None of the other patients observed showed such a marked platelet deficiency, and it would appear that its occurrence is rare in hemophilia, although reduction in the number of

TABLE 3—RESULTS OF EXAMINATION OF BLOOD OF SISTER OF CASE 1 AND OF MOTHER AND SISTERS OF CASES 2 AND 3

Case	Member of Family	Coagulation Time, Minutes		Prothrombin			Antithrombin		
		Pa-tient	Con-trol	Pa-tient	Con-trol	Quo-tient	Pa-tient	Con-trol	Quo-tient
1	Sister (M. R.)	23	—	9	10	0.9	17	19	0.9
2	Sister (Agnes McC.)	23	20	12	9	1.3	58	49	1.1
	Sister (Adeline McC.)	20	23	12	10	1.2	52	50	1.0
	Mother	16	19	14	10	1.4	20	25	0.8

these elements has been noted by some observers<sup>25</sup>. Of interest also is the fact that the prothrombin remained low even when the platelets had returned to a normal level. The relation of blood platelets to the origin of prothrombin will be considered in another connection.

DISCUSSION OF RESULTS

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with the experiments presented by other workers to prove that hemophilic blood contains less of this coagulation-inhibiting substance<sup>7</sup> On the whole, our work supports the conclusion that there is no marked difference between the absolute amount of antithrombin contained in hemophilic and in normal blood plasma, although it is clear that this

TABLE 4—RECORD OF LEUKOCYTIC AND PLATELET COUNTS FROM OCTOBER, 1913, TO OCTOBER, 1914, IN CASE 1

Date	Platelets*	W B C	Poly morpho nuclears, Per Cent	Large Round, Per Cent	Lympho cytes, Per Cent	Eosino phils, Per Cent	Remarks
10/ 9/13	280,000 (W & K) 211,000 (P)	3,900	63.6 67	3.6 2	31.8 31	1	
10/14/13	400,000 (W & K)	6,400	67	6	26	1	Bleeding time 1 min 5 sec
10/16/13	350,000						
10/20/13	860,000?	8,100	54	10	36		
10/23/13	456,000	7,000	60.4	4	35	0.6	Bleeding time 3 min 20 sec
11/ 4/13	324,600	5,200	59.6	4.3	36.1		
11/12/13		4,600	45	18	36		
11/13/13		6,700	59	5	34	1	
11/15/13		6,000	65	5	29		
11/17/13	416,000	6,400	63	7	30		
11/19/13		5,100	46	21	30	1	
11/21/13		3,600	49	17	23		
11/24/13		3,400	41.5	8.6	48.4	1	
12/ 1/13		7,200	47	4	47	2	
12/ 8/13		8,200	46	11	43		
12/18/13		7,000	50	10	40		
12/28/13		4,200	40	5	55		
1/ 6/14		3,400	38	4	58		
2/ 2/14		8,100	60	7.5	30		
2/13/14	372,000	6,200	54	15	26		
2/20/14	256,000	6,125	43	31	23	1	Bleeding time 5 min
3/ 8/14		5,380	40	10	46	3	
3/20/14	184,000	7,400	55	15	28		
4/ 2/14	160,000						
10/ 9/14		11,400	53	5	34	1	Bleeding time 4½ min
10/18/14		10,300	65	7.5	26	2	
Average		2,150	53				

\* The method of enumerating the platelets used is given wherever the exact technique employed is stated in the records. W and K means Wright and Kinnleutt's method. P means Pratt's method. For the most part one or the other of the two methods was used.

substance must be present in relative excess in hemophilia in proportion to the extent of diminution of the available prothrombin

The deficiency in the amount of prothrombin was demonstrated by the simple procedure already described of oxalating the plasma and then adding to it the optimum amount of calcium. Our studies make it possible to state with confidence that this procedure furnishes a reliable means of differentiating hemophilic blood from the blood of other hemorrhagic conditions. Although this element has been followed throughout various periods of the disease, at no time has it been found normal. It has been our experience that wide fluctuations

TABLE 5—RECORD OF LEUKOCYTES AND PLATELETS, CASES 2 AND 3

## CASE 2 (J McC)

Date	Platelets	W B C	Poly-morpho nuclears, Per Cent	Large Round, Per Cent	Lympho- cytes, Per Cent	Eosino- phils, Per Cent	Remarks
11/24/15		8,300	70	9	21		Roentgen ray exposures commenced 12/1 and ended 12/11
12/ 3/15	216,000	15,200	53	10	33	2	
12/13/15		11,800	64	12	24	1	
12/15/15	160,000						Bleeding time prolonged

## CASE 3 (D McC)

10/10/15		12,900	94	15	4		Roentgen ray exposures commenced 12/1 and ended 12/11
10/15/15	580,000	11,150	56	10	32	3	
10/22/15	192,000		70	8	21	1	
11/24/15		10,400	52	10	34	4	
12/ 3/15		13,000	53	6	40	2	
12/13/15		14,600	72	7	20		
12/15/15	204,000						

in the amount of prothrombin may exist during the hemorrhagic as well as during the interhemorrhagic periods of the disease, and that the degree of this defect bears no definite relationship to the severity of the clinical symptoms. This point is well illustrated by the observations in Cases 1 and 2. In both of these patients a less marked reduction of the circulating prothrombin was noted immediately after an attack of bleeding, but a similar increase in this factor has been observed also during the interhemorrhagic period. On the basis of the experimental evidence at hand, it is therefore impossible to make any definite statements concerning this point.

Although it can be stated with a fair degree of certainty that the proximate cause of the delayed coagulability is due to a diminution in prothrombin, the ultimate cause of the condition is still a matter of speculation. Some knowledge concerning this more fundamental problem can be gained from the studies on the origin of prothrombin. So far as is known at present, the circulating prothrombin of the blood plasma is furnished by the blood platelets. This fact is based on good experimental evidence. But it is difficult to bring these observations into harmony with the well-known fact that the number of blood plate-

TABLE 6—ALBUMIN, GLOBULIN, AND NONPROTEIN IN HEMOPHILIC BLOOD SERUM

Patient	Date	Total Protein Per Cent	Total Albumin Per Cent	Total Globulin Per Cent	Albumin, Per Cent of Total Protein	Globulin, Per Cent of Total Protein	Non protein Constitu- ents, Per Cent
G R, Case 1	11/10	7.3	5.4	1.9	74	26	10
	12/15	6.6	5.1	1.5	76	24	12
J McC, Case 2	10/28	6.9	5.2	1.7	75	25	11
	11/ 5	6.6	4.8	1.8	73	27	12
	12/ 3	6.4	5.3	1.1	82	18	10
D McC, Case 3	10/11	7.1	5.0	2.1	70	30	10
	11/ 1	7.0	4.2	2.8	60	40	10
	12/ 3	7.0	4.5	2.5	64	36	10
	12/15	7.6	5.0	2.6	65	35	11
A S, Case 4	10/29	7.2	5.3	1.9	73	27	10
	11/20	7.3	5.3	2.0	73	27	11
E O, Case 5	11/18	6.7	5.9	0.8	88	12	10
	12/20	6.6	5.5	1.1	82	18	10
Averages		6.9	5.1	1.8	73	26	10
Normal human serum*		7.94	6.20	1.74	78	22	10.9

\* The figures for the percentage concentration of serum albumin and serum globulin in normal human blood serum are the averages obtained by Tranter and Rowe (Jour Am Med Assn 1915 LV, 1433) on about thirty normal serums.

lets in hemophilia is normal. In explanation of this paradox, it has been assumed that the defect in question is attributable to a functional rather than to a numerical change in these elements. This assumption has received some experimental support from the recent work of Fonio.<sup>26</sup> As this worker has shown, platelets derived from hemophilic blood are less potent in hastening the clotting of such blood than are platelets obtained from normal blood. Fonio refers this defect of hemophilic platelets to a diminished thrombozym (thromboplastin) content, but it would appear that the evidence presented does not

26 Fonio A. Mitt a d Grenzgeb d Med u Chir, 1914 LVIII 313

establish with any certainty that this functional defect of hemophilic platelets may not be due to a diminution in their prothrombin content. For, as is well known, the solution of platelets when blood is shed facilitates clotting in two ways—first, by setting free prothrombin, and second, by liberating a thromboplastic substance which hastens coagulation by neutralizing the antithrombin present normally in the circulating blood.

Furthermore, in the solution of this paradox the possibility must be kept in mind that other factors besides the blood platelets may be concerned with the origin of prothrombin. For instance, it has been shown that although a considerable diminution in prothrombin may result from the destruction of myeloid tissue following benzol injections, no direct parallelism exists between this drop in prothrombin, the number of platelets, and the extent of bone marrow injury.<sup>27</sup> These experimental observations support the view that the maintenance of the prothrombin equilibrium of the blood depends only in part on the blood platelets. At the present time it is not possible to state what tissue or tissues besides the marrow may be concerned in the elaboration of prothrombin. Thus far experiments have given no support for or against the contention of Nolf<sup>8</sup> that liver cell activity is essential for prothrombin production.

#### THE EFFECT OF KEPHALIN AND OF THE ROENTGEN RAYS ON THE BLOOD IN HEMOPHILIA

Studies concerning the proximate cause of the delayed coagulability of hemophilic blood naturally suggest the idea that it might be possible to devise some means of supplying to the patient the element in which his blood is deficient. A rational therapy of this kind might be approached theoretically in one of three ways—first, by a readjustment of the prothrombin-antithrombin balance to a more normal state by the introduction of thrombin or its antecedent substance, prothrombin, directly into the circulation, second, by stimulating the tissues concerned with prothrombin elaboration to form more of this deficient factor, and lastly, by a neutralization of the relative excess of antithrombin by the injection of tissue extracts. Some attempts have already been made to modify the coagulability of the blood of healthy animals by means of some of these methods. Experiments of this nature have developed the very interesting fact that in health the blood or the body can protect itself within wide limits from the effects of such injections. For instance, Davis,<sup>28</sup> working in Howell's laboratory, has shown that solutions of pure thrombin may be introduced

<sup>27</sup> Hurwitz, S. H., and Drinker, C. K. *Jour. Exper. Med.*, 1915, **xxi**, 401.

<sup>28</sup> Davis, D. *Am. Jour. Physiol.*, 1911-1912, **xxix**, 160.



into the circulation in quantities that in the test tube would cause rapid and firm clotting and yet no harm be done. It is apparent, therefore, that a healthy animal can protect itself from the effects of substances which would endanger its life by the formation of intravascular clots. The nature of this defensive reaction consists, it is thought, in the formation within the organism of a compensatory amount of antithrombin to bind either the injected thrombin or to neutralize the tissue extracts introduced into the circulation. But we do not know with any certainty whether or not the same response can occur in pathological states in which the balance is already disturbed in the direction of an increased or decreased coagulability. Indeed, only few attempts have been made to modify by these means the blood in diseased conditions associated with a defect in the fibrin factors. Because of the meagerness of data on this point, it seemed worth while to study this phase of the subject on some of the patients under observation.

On the basis of some experiments which will be recorded in another paper, we studied the influence produced by the injections of kephalin and the effect of Roentgen irradiation on the blood in hemophilia. With regard to kephalin, preliminary experiments on healthy rabbits had shown that this substance could be introduced into the circulation either intramuscularly or intravenously without any untoward symptoms, and that the immediate effect of intravenous injections was an increase in the coagulability of the blood. This increased coagulability was only transitory, however, and was followed soon by a return of the blood to a normal state, or in a few instances by a decreased coagulability. The exposure of animals to suberythema doses of Roentgen rays, on the contrary, produced no perceptible increase in coagulability, although an examination of the blood for the separate factors disclosed a transitory rise in the circulating prothrombin. The temporary character of this reaction and its failure to decrease the coagulation time can be explained in the light of the defensive power of the organism considered in a previous paragraph. And although these experiments showed that the effect of the administration of kephalin and of exposure to the Roentgen rays produced only temporary changes in the condition of the blood, the possibility still remained that these agents might act differently in conditions like hemophilia. Accordingly we decided to try the effects of one or both of these measures on three of the patients.

In the first patient observations were made on the effect of kephalin therapy alone, whereas, both the second and third patients were treated with kephalin and with the Roentgen rays. Concerning the dosage of kephalin the preliminary experimental work had assured us that a considerable amount of this substance could be administered intra-

venously without any untoward symptoms. In some animals as much as 10 c.c. of a 1 per cent solution were introduced into the ear vein without ill effects. Although some workers<sup>29</sup> have investigated the coagulation accelerating effect of intravenous injections of saline extracts in hemophilia, we did not feel that such injections were entirely devoid of danger, and we have, therefore, no data to present on this point. It will be noted from the clinical records that only the oral, subcutaneous and intramuscular modes of giving kephalin were used. The first method was early abandoned because it proved ineffective, and subcutaneous injections were discarded because they were painful. Intramuscular injections, on the other hand, were not followed by any local or constitutional reaction, and these were used exclusively in the second and third patients.

In the choice of the proper dosage for the Roentgen-ray exposure, we were guided largely by following the formed elements in the blood. As is well known from the work of recent observers,<sup>30</sup> small and large doses of Roentgen rays have antagonistic effects on the blood-forming organs, the former exert a stimulating action and the latter a destructive action. For our purposes, it was determined that one-twentieth of an erythema dose applied to the long bones at the stated intervals produced the desired stimulation of the blood-forming organs as evidenced by the rise in leukocytes. In one of the patients (Case 3), a drop in the platelet count and a prolongation of the bleeding time after the eighth exposure showed that the rays were beginning to act destructively, and this served as an indication for stopping the treatment.

The results of both of these forms of therapy have been presented for the most part in the clinical histories and in the tabulated results. Only a few points deserve further consideration. In order to avoid criticism, it is desirable in the first place that judgment regarding the results of any therapeutic measure used to control hemorrhage be guided by some criteria. Apart from all other considerations, it seems fair to assume that a therapeutic measure is successful only if it causes a cessation of the bleeding, and so affects the disease process itself that the coagulability of the blood is increased. On the basis of such criteria, it is not possible to make any great claims for Roentgen-ray therapy and for kephalin injections in the constitutional treatment of hemophilia. Concerning Roentgen-ray treatment, it is safe to conclude that small stimulating doses do not alter in any way the condition of the blood in hemophilia. It is not possible to say at

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<sup>29</sup> Schloessmann, H. Beitr. z. klin. Chir. 1912 LXXIX 492.

<sup>30</sup> Hemecke, A. Deutsch. Ztschr. f. Chir., 1905 LXXVIII 196. Duke, W. W. Variation in the Platelet Count, Its Cause and Clinical Significance. Jour. Am. Med. Assn., 1915, LX 1600.

present whether these negative results in hemophilia, in contrast with those obtained in healthy animals, are due to a lack of response on the part of the blood-forming organs or whether more prolonged and more intensive treatment is necessary to effect any changes

Furthermore, the especial therapeutic use of kephalin has not been found to lie in its influence on the disease process, for we have not been able to show that this substance administered intramuscularly in the dosage employed by us effects any noticeable change either in the coagulability of the blood or in the prothrombin-antithrombin balance Only once did the opportunity arise to determine the value of intramuscular injections in the control of external bleeding (Case 2) But in this instance, it will be recalled, the injections were combined with the application of kephalin to the wound surface Because similar injections in other patients had failed of effect, we are inclined to attribute the early arrest of bleeding in this case to the local action of the kephalin Of its great hemostatic properties we have become convinced from observations on its coagulation accelerating action on whole blood in the test tube as well as when applied locally to bleeding surfaces And although similar properties have been claimed for other tissue extracts, we believe that its thermostability gives kephalin a decided advantage over saline or aqueous extracts in that it can be sterilized without weakening its action <sup>31</sup> It is to be hoped, therefore that kephalin will prove of real value in the treatment of uncontrollable hemorrhages from external wounds so frequently met with in hemorrhagic conditions

SUMMARY

- 1 No alteration has been observed in the reaction of hemophilic blood In all of the patients studied, the hydrogen-ion concentration of the serum showed the normal variation
- 2 No abnormality exists in the third phase of coagulation clot formation is slow, but the clot, when once formed, shows normal retractile power
- 3 The percentages of serum albumin, serum globulin, and total protein of hemophilic serum do not show wide variations from the normal
- 4 The essential defect of hemophilic blood, which accounts for its delayed coagulability, is a diminution of the circulating prothrombin The other two fibrin factors, antithrombin and fibrinogen, are present in normal amounts Wide fluctuations may be observed in the pro-

<sup>31</sup> Howell has called attention to this property of saline or aqueous extracts He has shown that heating such solutions precipitates the protein, together with the active phosphatid But if the phosphatid is first extracted with ether, the residue may be dissolved in water and the solution is unaffected by boiling (*Am Jour Physiol* 1912-1913, *XXXI*, 1)

thrombin content of hemophilic plasma both during the hemorrhagic and interhemorrhagic periods. No definite relationship can be shown to exist between the extent of the prothrombin deficiency and the gravity of the clinical symptoms.

5 The method suggested by Howell of first oxalating the blood and then recalcifying with an optimum amount of calcium gives a simple and reliable means of diagnosing hemophilia and of differentiating it from other hemorrhagic conditions. It is to be recommended that this test be carried out preliminary to any operation on a patient exhibiting the hemophilic tendency.

6 Oral, subcutaneous and intramuscular injections of kephalin have no effect on the disease process.

7 Kephalin applied locally to the bleeding wounds of hemophiles brings hemorrhage to an early arrest. Because of its great hemostatic properties and its thermostability kephalin deserves an important place in the treatment of bleeding from external wounds.

8 Suberythema doses of Roentgen rays do not influence the disease process. No alteration was noted either in the coagulability of the blood or in the prothrombin-antithrombin balance.

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# THE SIGNIFICANCE OF THE URIC ACID, UREA AND CREATININ OF THE BLOOD IN NEPHRITIS\*

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In an earlier communication<sup>1</sup> attention was called to the practical value of the estimation of the creatinin of the blood in nephritis. It was pointed out that an appreciable retention of creatinin indicated a grave impairment in the functional condition of the kidney, for the reason that creatinin is normally the most readily eliminated of the three nitrogenous waste products—uric acid, urea and creatinin. In contrast to creatinin, however, uric acid is apparently eliminated by the kidney with difficulty. It is, therefore, not surprising that conditions of moderately decreased kidney permeability should be encountered, in which only the concentration of the uric acid of the blood should be raised. This appears to be the case in gout and early interstitial nephritis. In the present paper it is our intention to lay emphasis on those cases in which the permeability of the kidney is not sufficiently impaired to cause a marked retention of creatinin.

The deductions which Sir A. B. Garrod<sup>2</sup> drew from his work in this connection in 1848 are very interesting, and their general harmony with current views surprising when one considers the methods then available. His conclusions (referring to Bright's disease and the albuminuria following scarlatina) were

1 Uric acid is always present in the blood in albuminuria. The quantity, however, greatly varies: when the functions of the kidneys are much impaired it exists in quantities almost as great as in gout; in other cases, its amount is small, but it usually exceeds that found in ordinary blood. 2 Urea always exists in large quantities in this blood (a fact which has long since been proved) and no relation is found between the amounts of urea and uric acid. 3 The kidneys are always deficient in their power of throwing off urea, but with regard to uric acid, their excreting function may be impaired or not.

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1 Myers V. C. and Lough W. G. The Creatinin of the Blood in Nephritis—Its Diagnostic Value. *THE ARCHIVES INT. MED.*, 1915, **xxi**, 536.

2 Garrod, A. B. Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease. *Medical-Chirurgical Trans.*, 1848, **xxxiii**, 83.

Garrod's paper apparently aroused considerable discussion, for he appended the following

Postscript July 26, 1848 At the discussion which ensued after the reading of the above paper to the society, some remarks were made which implied that I was understood as considering gout to be entirely dependent upon the power of the kidney for the excretion of uric acid, such, however, is not my opinion, and at present I do not wish to advance any hypothesis as to the cause and nature of gout, considering that many further researches should be made on the subject before a theory of the disease could be advanced with safety

The investigation of von Jaksch<sup>3</sup> in 1896 gave confirmation to the observations of Garrod on the retention of uric acid in nephritis

Von Noorden<sup>4</sup> gives a most interesting discussion on the uric acid content of the blood in gout and nephritis He writes

The primary cause of the uric acid retention in gout lies in the kidney, according to Garrod Recently Levison and Luff, and, with certain reservations, also Strauss, have advocated the same view Levison and Luft showed, in a very large series of postmortems in Denmark and in England, that in cases of interstitial nephritis, uric acid deposits in the articular cartilages are very frequently found, although the condition was not suspected during life Stripped of all unnecessary detail, this means that the retention of uric acid in the blood and the remaining phenomena of gout are the results of primary disease of the kidney In certain cases both nephritis and gout are amenable to clinical diagnosis In other cases, nephritis, and in still others the uric acid diathesis, remain for a long time, perhaps even up to the end of life, clinically free from symptoms and unrecognized

The figures of Levison and Luff show, in the first place, that nephritis and gout occur in the same individual more frequently than was formerly assumed They recall to us the facts that harmful influences, especially alcoholism and saturnism, and also heredity, play an acknowledged part in the etiology of both diseases

It appears that continuous overloading of the blood with uric acid (nephritis) does not necessarily lead to gout, and, moreover, that this overloading is not followed by uric acid deposition without the accession of another still unknown, specific gouty factor

No noteworthy advance in this connection, however, was made until the advent of Folin's new method<sup>5</sup> The work of Folin and Denis,<sup>6</sup> and others employing their methods, has been principally to confirm the views advanced by Garrod nearly seventy years ago, although with the quantitative data now available more definite conclusions have been possible Folin and Denis and the authors<sup>7</sup> have reported cases of uremia with marked retention of uric acid, urea and creatinin Twelve cases have come under our observation with more than 10 mg of uric

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3 Von Jaksch, R Beitrag zur Kenntnis der Uricacidämie der Nephritiker Zentralbl f inn Med, 1896, xvii, 545

4 Von Noorden, C Metabolism and Practical Medicine, 1907, iii, 669

5 Folin, O, and Denis, W Jour Biol Chem, 1913, xiii, 469

6 Folin and Denis Jour Biol Chem, 1913, xiv, 29, 1914, xvii, 487

7 Myers, V C, and Fine, M S Jour Biol Chem, 1915, xx, 391

acid per 100 c c of blood, in one case 27 mg , still no gouty symptoms were evident It is of interest regarding the uric acid that early in the disease the values observed may be somewhat higher (7 to 8 mg ) than at a later stage (5 to 6 mg ), although during the last days of life the amount may very markedly increase, this being coincident with an accumulation of creatin in the blood

Folin and Denis<sup>8</sup> noted that in the severest cases of uremia there was only a slight increase in the blood ammonia, and that it was likewise only these cases in which a marked retention of creatinin occurred From this they conclude

The figures obtained indicate that the human kidney removes the creatinin from the blood with remarkable ease and certainty The completeness of the creatinin excretion is, in fact, exceeded only by the still more complete removal of the ammonium salts

It is possible that other factors, such as acidosis and the formation of urea, may have some relation to the increase in the ammonia of the blood, but the increased blood creatinin is obviously due to one cause, namely, the markedly impaired permeability of the kidneys Since creatinin is the most readily eliminated of the nitrogenous waste products (creatinin, urea and uric acid) and uric acid the most difficultly eliminated, as indicated above, urea must obviously stand in an intermediate position (see Table 3) That this should be the case seems quite plausible when we consider the ease of excretion of these constituents as determined from a comparative nitrogen partition of normal urine and blood Uric acid nitrogen forms 2 per cent of the nonprotein nitrogen of both urine and blood, urea nitrogen about 85 per cent in urine, but 50 per cent in blood, and creatinin nitrogen 5 per cent in urine, but only 2 per cent in blood It is quite possible that the physical properties and concentration of these constituents in the blood may play an important rôle in the ease with which the kidney eliminates them

It has been possible to select from a large series of miscellaneous blood analyses a considerable number of cases with decidedly high figures for uric acid, but with only slightly increased urea concentrations and with creatinin figures scarcely above the normal limits As was pointed out in a previous communication,<sup>1</sup> a creatinin of over 5 mg per 100 c c of blood appears to indicate an early fatal termination It was the object of the present study to secure cases of the same type, but at an earlier stage in the disease, when changes in diet and mode of living might be of some aid in withholding for a time the uremia, from which most of these patients ultimately die

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<sup>8</sup> Folin and Denis Jour Biol Chem 1914, LVII, 487

## METHODS EMPLOYED

Before proceeding to a discussion of our data on this subject, it is fitting that a brief description should be given of the methods we have employed for the estimation of uric acid, urea and creatinin in blood. Folin has recently raised certain objections to his own technic<sup>9</sup> for the estimation of uric acid in blood. We have embodied the suggestions of Benedict<sup>10</sup> in our application of the method, and are confident of the reliability of the results. The Duboscq colorimeter has generally been employed for the estimation of the uric acid and creatinin, although in the case of urea, the Hellige instrument has frequently been used. For the estimation about 20 c.c. of oxalated blood are needed. To avoid complications from the influence of food and possible changes in blood volume, the blood has generally been taken in the morning before breakfast.

*Uric Acid*—Ten cubic centimeters of the well-mixed blood are pipetted into a casserole of about 375 c.c. capacity and approximately 5 volumes of hundredth-normal acetic acid added. The mixture is heated over a water bath and finally brought to a boil over a free flame, stirring continuously. About 4 c.c. of fairly thick alumina cream<sup>11</sup> are added with continuous stirring for a few minutes. The sides of the dish are washed down from time to time with hot water and the mixture then filtered through a hardened filter paper. The coagulum is returned to the casserole with about 150 c.c. of hot water, heated and filtered through the same paper. The combined filtrates are evaporated to 1 or 2 c.c. (the material should be protein-free) and transferred to a 15 c.c. conical centrifuge tube, washing the casserole with 2 or 3 small portions of hot water but keeping the volume at or below 10 c.c.

About 15 drops of ammoniacal-silver-magnesium mixture<sup>12</sup> are now added, the tube shaken and placed in a cool place (refrigerator) for about 15 minutes to allow for the precipitation of the purins. The tube is centrifuged, the supernatant liquid decanted off and allowed to rest in inverted position for about five minutes. The tip of the tube is then wiped with filter paper and the ammonia allowed to volatilize (may be facilitated with suction).

For the development of the color prepare a 100 c.c. graduated cylinder for the standard and a 50 c.c. cylinder for the unknown. Five c.c. of the uric acid standard<sup>13</sup> (5 c.c. = 1 mg. of uric acid) are pipetted into the 100 c.c. cylinder

9 Folin, O. and Bell, R. D. Proc. Am. Soc. Biol. Chem., 1915

10 Benedict, S. R. Jour. Biol. Chem., 1915, xx, 629

11 Prepared by precipitating an 8 per cent solution of aluminum acetate in acetic acid with sodium bicarbonate, carefully washing with a large volume of distilled water by decantation several times, then filtering.

12 The ammoniacal-silver-magnesium solution is prepared by mixing 70 c.c. of 3 per cent silver nitrate solution, 30 c.c. of magnesia mixture and 100 c.c. concentrated ammonia. Any turbidity which may develop is filtered off. Magnesia mixture is prepared by dissolving 35 gm. magnesium sulphate and 70 gm. ammonium chloride in 280 c.c. distilled water and then adding 140 c.c. concentrated ammonium hydroxide.

13 The standard uric acid solution is prepared as follows. Dissolve 9 gm. pure crystalline hydrogen disodium phosphate and 1 gm. dihydrogen sodium phosphate in 200 to 300 c.c. hot water. Filter and make up to about 500 c.c. with hot water. Pour this warm, clear solution on 200 mg. uric acid suspended in a few cubic centimeters of water in a liter volumetric flask. Agitate until completely dissolved. Add at once exactly 14 c.c. glacial acetic acid. Make up to 1 liter, mix and add 5 c.c. chloroform. Five cubic centimeters of this solution are equivalent to 1 mg. uric acid. The solution should be freshly prepared every two months.



To the standard are added 2 drops of 5 per cent potassium cyanid, 2 c c of Folin-Macallum reagent,<sup>14</sup> 20 c c of saturated (22 per cent) sodium carbonate, and, in about one minute, water to the 100 c c mark. To the precipitate in the centrifuge tube are added 1 or 2 drops of the potassium cyanid, 2 c c of the Folin-Macallum reagent and 15 or 20 c c of the saturated sodium carbonate, depending on whether the color is subsequently diluted to 50 or 100 c c. After forty to sixty seconds dilute with water until the intensity of the color is similar to the standard and then match in the Duboscq colorimeter. The prism of the standard may conveniently be set at the 10 mm mark.

*Urea*—The method is based on the suggestions of Marshall<sup>15</sup> and Van Slyke.<sup>16</sup> Into a test tube (of such size that it will just slip into a 100 c c cylinder) are introduced 1 c c of 10 per cent urease solution, or about 0.1 gm of the dry enzyme,<sup>17</sup> and then 1 to 2 c c of water. Two cubic centimeters of blood are now added with an Oswald-Folin pipet and the tube incubated in a beaker of water at 50 C for about one-half hour. At the end of this time 3 to 4 drops of caprylic alcohol or 1 c c of amyl alcohol are added to prevent foaming in subsequent aeration. Into a 100 c c graduated cylinder, without lip, are added 15 c c of distilled water and 2 drops of 10 per cent hydrochloric acid. This is now closed with a two-hole stopper having a glass tube passing nearly to the bottom of the graduate. The tube is sealed at the lower end, but contains a number of small holes to aid in the complete absorption of the ammonia (Folin). To the test tube containing the digested blood is carefully added an equal volume of saturated sodium carbonate, or better still, potassium carbonate, the solution being allowed to run underneath the blood. The tube is now immediately inserted in a 100 c c (ungraduated) cylinder and a two-hole stopper is used containing one glass tube which passes nearly to the bottom of the tube. This is now connected on one side with a wash bottle containing dilute sulphuric acid and on the other with the graduated cylinder containing the dilute acid for the absorption of the ammonia. The ammonia of the blood is now transferred to the cylinder containing the weak acid, by vigorous aeration for twenty to thirty minutes. At the end of this time the outfit is disconnected and nesslerization (Folin) carried out in the graduated cylinder, dilution being made according to the amount of ammonia present.

Into a volumetric flask of 100 c c capacity, if the Duboscq colorimeter is to be used, are pipetted 5 c c of ammonium sulphate or ammonium chlorid solution containing 1 mg of nitrogen.<sup>18</sup> About 50 to 60 c c of distilled water are next added. Ten cubic centimeters of modified Nessler's solution<sup>19</sup> are now diluted about five times with distilled water, and of this 20 to 25 c c added to the standard solution, which is then made up to the mark with water. At the

14 The reagent, as modified by Prof S R Benedict (private communication), is prepared by boiling 100 gm sodium tungstate, 20 c c concentrated hydrochloric acid and 30 c c 85 per cent phosphoric acid in 750 c c distilled water for two hours, preferably under a reflux condenser, and then making up to 1,000 c c with water.

15 Marshall, E K. Jour Biol Chem, 1913, xv, 487.

16 Van Slyke, D D, and Cullen, G E. Jour Biol Chem, 1914, xix, 211.

17 Prepared by Dr I F Harris, Bronxville, N Y.

18 The solution may be prepared by dissolving 0.944 gm ammonium sulphate or 0.764 gm ammonium chlorid of the highest purity in distilled water and making up to 1,000 c c.

19 For the modified Nessler's solution, place 100 gm mercuric iodid and 50 gm potassium iodid, both finely powdered, in a liter volumetric flask and add about 400 c c water. Now dissolve 200 gm potassium hydroxid in about 500 c c water, cool thoroughly and add with constant shaking to the mixture in the flask, then make up with water to the liter mark. This usually becomes perfectly clear. Keep at body temperature over night, or until the yellowish white precipitate which may settle out is thoroughly dissolved and only a small amount of dark brownish red precipitate remains. The solution is now ready to be siphoned off and used.

same time 7 to 8 cc of the freshly diluted Nessler's solution are added to the unknown solution and the volume made up to 25 cc in the graduate, unless a high content of urea nitrogen is indicated, in which case more Nessler's solution (up to 25 cc) and a dilution to  $33\frac{1}{3}$ , 50, 100 cc or even more may be needed to make the color of the unknown of approximately the same intensity as the standard. The colorimetric readings should be made without delay, the standard prism being set at the 10 or 15 mm mark.

*Creatinin*—The technic for the creatinin estimation is briefly<sup>1</sup> as follows: 5 cc of the well-mixed blood are treated with 20 cc of water (4 volumes) in a 50 cc centrifuge tube. After the corpuscles have been laked, about 1 gm of dry picric acid is added, and the mixture stirred at intervals with a glass rod until it is a light yellow. When the protein precipitation is complete, the tube is centrifuged and the supernatant fluid filtered through a small filter paper. To 10 cc of the filtrate is added 0.5 cc of 10 per cent sodium hydroxide, and a similar amount of alkali added to 10 cc of standard creatinin in saturated picric acid.<sup>20</sup> It is best to make up simultaneously three standards containing 0.3, 0.5 and 1.0 mg creatinin to 100 cc of picric acid. The tube corresponding most nearly with the unknown is used as standard, the prism of the Duboscq colorimeter being set at either the 10 or 15 mm mark. Allow ten minutes for the color to develop before comparing.

#### DISCUSSION

Although considerable attention has recently been given to the urea and nonprotein nitrogen of the blood in nephritis, scant consideration has been accorded the uric acid and creatinin. It is true that the greater part of the waste nitrogen is eliminated in the form of urea, but it does not necessarily follow from this that data on uric acid and creatinin are unimportant and uninteresting. In fact, Folin's<sup>21</sup> classic work of ten years ago on the urine, by way of comparison, would suggest that the reverse might be true. Outside of Folin's laboratory and our own, practically no work has been reported in which estimations of the uric acid, urea and creatinin have been simultaneously carried out on pathological bloods. We do not believe that it is possible to make satisfactory deductions regarding nitrogen retention from the urea or nonprotein nitrogen determinations alone, as many have recently done.

In the most recent paper of Folin and Denis<sup>22</sup> dealing with blood uric acid, these authors point out the importance, from a diagnostic standpoint, of having the uric acid estimation accompanied by that of nonprotein or urea nitrogen. Their data give figures for nonprotein nitrogen and uric acid. It seems unfortunate to us that they did not include figures for urea and creatinin. The determination of the urea concentration of the blood is, we believe, of more value than that of the nonprotein nitrogen, for the reason that it represents the reten-

<sup>20</sup> Creatinin may now readily be prepared perfectly pure by the admirable method of Benedict, *Jour Biol Chem*, 1914, xxiii, 183.

<sup>21</sup> Folin, O. *Am Jour Physiol*, 1905, xiii, 45.

<sup>22</sup> Folin, O., and Denis, W. *The Diagnostic Value of Uric Acid Determinations in Blood*, *THE ARCHIVES INT MED*, 1915, xvi, 33.

TABLE 1--BLOOD ANALYSES IN "EARLY INTERSTITIAL NEPHRITIS"

Date 1915 16	Case	Age	Sex*	Blood Analysis			Phthal cin 2 Hour Out put	Blood Pressure		Urine		Remarks
				Urea Acid, Mg to 100 cc	Urea N, Mg to 100 cc	Creatinin, Mg to 100 cc		Systolic	Diastolic	Albumin	Casts	
8/11	1 J J <sup>1</sup>	65	♂	9.5	25	2.5	13	185	90	+	+	Apparently early chronic interstitial nephritis
9/25				8.4	37	2.7		150	85			
1/14				5.0	37	3.9		130				
9/21	2 D D	52	♂	8.7	20	3.6	20	100	87	+	+	Cirrhosis of liver and chronic interstitial nephritis, severe alcoholism Pulmonary tuberculosis Prostatic hypertrophy
9/14	3 L G	28	♂	7.2	22	2.1		120	95	-	+	
9/22	4 H J	60	♂	7.2	18	2.5				+	-	
6/7	5 D S	56	♂	7.1	16	2.0	26			-	+	Apparently early chronic interstitial nephritis
7/21				6.6	24	3.3		185	110			
9/28				6.3	18	2.1						
8/13	6 J Ju	53	♂	7.0	33	2.6	43	115	80	+	pus	Chronic constipation, alcoholism
11/16				6.8	20	1.8						
11/30				6.3	22	2.5		140	80			
6/15	8 M S	41	♀	6.7	22	1.5	53	120	75	++	-	Oncenoma of stomach, metastases to liver, chronic interstitial nephritis, pneumonia four months previous to admission, painful urination, loss of weight Frontal headaches, scarlet fever and diphtheria as a child Typhoid fever, headaches Pulmonary tuberculosis, tuberculosis of kidney, frequent urination, pain in bladder, headache, dizziness and fainting spells Hypothyroidism, chronic interstitial nephritis, increasing weight, pain in lumbar region
9/14	9 G P	27	♂	6.7	14	2.4	62	130	90	+	+	
9/17	10 H L	23	♂	6.5	16	2.7	53	130	90	++	+	
8/3	11 O Ma	54	♂	6.3	31	2.0	45			-	-	
8/31				4.2	20	1.9		150	90			
9/21				6.3	23	2.4						

9/11	13 M R	69	♂	63	15	25	128	84	1+	—	Myocarditis, dyspnea, edema of legs, pneumonia two years ago, moderate alcoholism Prostatic hypertrophy
9/10	14 Ja O	69	♂	60	36	21	50		++	—	
10/18	15 L J	59	♂	58	45	30	Trace	85	+	pus	Tubes dorsalis, pyelitis, impairment of vision
10/26	16 J T	55	♂	56	30	16	33	85	+	+	Diabetes, cataract of right eye, mild chronic interstitial nephritis
8/10	17 E H	41	♂	56	13	21	45	65	—	—	Pericarditis, edema of feet and ankles, moderate alcoholism
9/21	18 S S	47	♂	55	25	30		95	++	+	Lobar pneumonia, scarlet fever as a child, pericarditis
6/11	19 T S	49	♂	55	24	33	62	85	+	+	Circinoma of larynx, chronic interstitial nephritis, chancre 29 years ago, Wassermann —
10/12	20 F D	45	♂	55	12	25	37	120	—	+	Chronic interstitial nephritis, pain in back, radiating to right thigh, mild grade of optic neuritis
8/ 3	21 F S	20	♀	55	11	27	40	95	++	++	Acute parenchymatous nephritis, following administration of salvarsan four months previously, generalized edema, frontal headaches, Wassermann ++
4/15	22 O Mo	54	♂	54	15	23	36	164	+	+	Chronic diffuse nephritis, myocardial insufficiency, Wassermann ++++, edema of abdomen and chest
4/27				36	16	29					Syphilis, fainting spells, headaches
9/ 7	23 S P	24	♀	52	15	25	60	92	+	— pus	
10/26	24 J A	32	♂	50	21	20	28	60	+	+	Chronic endocarditis, arthritis, palpitation of heart, dyspnea
11/ 5	25 F T	47	♀	50	14	14	52	90	—	—	Hyperthyroidism, general weakness, loss of weight, bronzing of skin, scarlet fever as a child, typhoid fever
11/19	26 K W	49	♀	50	22	25	28	110	++	+	Chronic endocarditis, chronic interstitial nephritis, decreased urinary output, dyspnea, scarlet fever as child
12/ 8				42	19	16	37				

\* ♂ signifies male, ♀ signifies female

tion of a definite compound, and, further, is more easily and more accurately determined. Where possible, however, both determinations are desirable. Folin and Denis divide their cases into the four mathematically possible groups, namely, cases with the uric acid and non-protein nitrogen of the blood, both normal, cases with normal uric acid and high nonprotein nitrogen, cases with high uric acid and normal nonprotein nitrogen (gout), and cases with high figures for both uric acid and nonprotein nitrogen (nephritis). The classification they have employed is obviously valuable, although we believe the "staircase effect" of the retention of uric acid, urea and creatinin, brought out in our Table 3 is even more valuable, particularly as regards the so-called uric acid bloods. In agreement with Folin and Denis, we have likewise observed cases with moderately high figures for nonprotein and urea nitrogen but with normal figures for uric acid. These cases belong to quite a different group (some of them are cases of parenchymatous nephritis), and will not be discussed at present.

It will be evident from the present paper that there are many cases which have only a slight or moderate retention of urea, but in which there is a very marked retention of uric acid (Table 3, Groups I and II). We might refer to other cases in which there was present, in addition, a marked retention of urea, but in which the creatinin retention was comparatively slight (Table 3, Group III). In the cases of the latter group the prognosis from the urea alone would have been far different from that made in the light of the blood creatinin. Still other cases might be mentioned in which a greater retention of creatinin was present and proved the more valuable diagnostic sign.<sup>1</sup> The determination of uric acid, urea and creatinin obviously gives a survey of the character of nitrogenous retention that would not be possible from the urea alone. Other tests may, of course, prove of value. Thus, in many cases of severe nephritis, the acidosis may be a factor of greater moment than the nitrogen retention, as we have recently observed with the aid of Van Slyke's apparatus for determining the carbon dioxide combining power of the blood.

It may be well at this point to recall that the normal range of these nonprotein nitrogenous blood constituents is, for uric acid, 2 to 3 mg, for urea nitrogen, 12 to 15 mg, and for creatinin, 1 to 2.5 mg per 100 cc of blood. An inspection of Tables 1 and 2 shows uric acid figures between 5 and 10 mg. In most instances the figures for urea nitrogen are likewise increased, the majority of observations being between 20 and 30 mg per 100 cc of blood. The urea retention is, however, nothing like that encountered in more advanced cases of interstitial nephritis, as shown in Table 3. The figures for creatinin, on the other hand, are nearly all very close to, or only slightly above, the normal limits.

The data of Table 1 give the results of a series of twenty-six cases<sup>23</sup> in which the concentration of the blood uric acid is decidedly increased without a corresponding increase in the urea or creatinin. Some of these cases show symptoms which, in general, are characteristic of "early interstitial nephritis." In other cases, although the nephritis was not the predominant clinical condition, it would appear that the systemic disturbances resulting from, or associated with, a variety of conditions, such as tuberculosis, typhoid fever, pneumonia,

TABLE 2—EVIDENCE OF "INTERSTITIAL NEPHRITIS" IN FOUR CASES OF DIABETES (THREE FATAL) AS SHOWN BY THE EXAMINATION OF THE BLOOD<sup>24</sup>

Date 1915-16	Case	Age	Sex	Sugar of Blood, Per Cent	Sugar of Urine, Per Cent	Uric Acid, Mg per 100 c c of Blood	Urea N, Mg per 100 c c of Blood	Creatinin, Mg per 100 c c of Blood	CO <sub>2</sub> * Combining Power of Plasma, c c per 100 c c
10/29	L F <sup>1</sup>	52	♀	0.80	2.2	10.5	55	2.1	37
10/30				1.10	0.6				31
4/10	M W <sup>2</sup>	53	♂	0.37	1.7	6.0	18	2.0	
4/17				0.98	1.6				
2/4	M S <sup>3</sup>	38	♀	0.53	1.3	5.0	44	2.3	49
8/26	B S <sup>4</sup>	46	♀	0.42	3.6	7.6	28	4.7	12

\* Corrected values

1 Duration of disease, several years, no coma until day of death, October 30, small amount of albumin in urine of October 26, 27 per cent of sugar, only faint trace of acetone in urine

2 Gangrene of toes at times during the last five years, glucosuria very severe early in the disease but later improved, systolic blood pressure 150 to 165 mm, phthalein output 44 per cent, moderate amount of albumin in urine of April 10, at death (April 18) urine showed only small amount of acetone, uremic symptoms thirty hours before death and about six hours previous to last blood analysis

3 Shortness of breath, vomiting, increased frequency of urination, cloudy urine, history of scarlet fever, blood pressure 125 to 85, urine showed from faint trace to small amount of albumin, sugar, 1.0 to 1.5 per cent, trace of acetone, no casts found, phthalein output 13 per cent

4 Patient entered hospital in coma and died several hours later, urine contained very large amounts of albumin, acetone and diacetic acid, and many granular casts

carcinoma, cardiac disorders, chronic alcoholism, etc, exerted the same influence on the kidney. It is not improbable that similar factors are at work in gout and the apparently uncomplicated cases of interstitial nephritis.

The data recorded in Table 2 are likewise of interest in this connection, since they clearly demonstrate a similar state of affairs in four

23 For the opportunity of studying the majority of these cases we are under obligations to the director of the Medical Department, Dr Edward Quintard. We are also indebted to Drs Samuel Lloyd, J Bentley Squier, Arthur F Chace and Robert H Halsey for a number of interesting cases which they have brought to our attention.

TABLE 3—URIC ACID, UREA N AND CREATININ OF BLOOD IN GOUT AND VARIOUS STAGES OF NEPHRITIS

Date 1913-16	Case	Age	Sex*	Diagnosis	Present Condition	Uric Acid, Mg to 100 cc of Blood	Urea N, Mg to 100 cc of Blood	Creatinin, Mg to 100 cc of Blood	Phthl aln Output 2 Hrs	Systolic Blood Pres- sure	Urine			
											Albumin	Casts		
9/ 3	M K	49	♀	I Typical case of gout	Unchanged	95	13	11	48	230	+	—		
10/ 5	T B	57	♂			84	12	22	35	164	—	+		
10/ 6	L J	43	♂			72	17	24		200	—	—		
10/ 6	C P		♂			68	14	17						
8/11	J Ja	65	♂	II Apparently early cases of chronic interstitial nephritis	Unchanged	95	25	25		185	+	+		
9/25						80	37	27	13	150				
1/14						50	37	30		130				
6/ 7						71	16	20						
7/21	D S	56	♂			66	24	13	26	185	—	+		
9/28						63	18	21	43					
9/21						52	♂	87	20	36			20	100
8/13	J Ju	58	♂			70	33	26		175	+	+	—	
8/ 3	O M	54	♂			63	31	21	23	150	—	—	—	
1/ 6	L P	57	♂					80	80	18	0	210	++	++
3/ 1								40	17	20	10	170		

1/23 5/21	J P	34	♂	III Moderately severe cases of chronic interstitial and chronic diffuse nephritis	Improved	{ { { {	83 53 95 25	72 21 44 19	32 19 35 19	25 43 38 52	238 145 210 120	{ { { {	++ ++ ++ ++
1/15 1/28	W O	49	♂			{ { { {	95 25 77 67	44 19 67 17	35 19 31 16	38 52  10	210 120 165 200	{ { { {	++ ++ ++ ++
8/6 10/1	L B	32	♀			{ { { {	77 67 83 65	67 17 39 24	31 16 29 30	 10  10	165 200 200 200	{ { { {	+ ++ ++ ++
8/7 8/24	L H	39	♀			{ { { {	83 65 224 150	39 24 236 240	29 30 167 205	10 10 0 23	200 200 210 225	{ { { {	++ ++ ++ ++
4/11	E O	50	♀	IV Typical terminal cases of chronic interstitial nephritis with uremia	Died	{ { { {	224 150 143 130	236 240 263 90	167 205 222 111	0 23 0 0	210 225 220 265	{ { { {	Pus ++ ++ ++
3/23	T D	34	♂			{ { { {	150 143 130 87	240 263 90 144	205 222 111 110	23 0 0 Trace	225 220 265 225	{ { { {	++ ++ ++ ++
1/25	S H	37	♂			{ { { {	143 130 87 87	263 90 144 144	222 111 110 110	0 0 0 Trace	220 265 225 225	{ { { {	++ ++ ++ ++
5/28	M O	8	♀			{ { { {	130 87 87 87	90 144 144 144	111 110 110 110	0 0 0 Trace	265 225 225 225	{ { { {	++ ++ ++ ++
4/15	J W	34	♂			{ { { {	87 87 87 87	144 144 144 144	110 110 110 110	Trace Trace Trace Trace	225 225 225 225	{ { { {	++ ++ ++ ++

\* ♂ signifies male, ♀ signifies female  
The cases in Group I require no further comment here, while for Group II reference may be made to the same cases in Table 1  
The following remarks may be made concerning the cases in Group III  
L P—Chronic interstitial nephritis with uremia, marked edema of feet and ankles previous to admission, thickening of arterial walls, left hospital improved  
J P—Chronic diffuse nephritis, Wassermann +++++, generalized edema, left hospital improved  
W O—Chronic diffuse nephritis, chronic alcoholism, severe headache, mild generalized edema, probable edema of brain, severe acidosis on admission as shown by carbon dioxide combining power of blood (Van Slyke), improving  
L B—Acute parenchymatous nephritis, pulmonary tuberculosis, pericarditis, edema of feet, ankles and face, left hospital improved  
L H—Chronic interstitial nephritis, mitral regurgitation, dyspnea, oedipital headaches, left hospital improved  
The cases in Group IV need no comment The blood analyses reported were those made shortly preceding death



advanced cases of diabetes<sup>24</sup> In the first case it will be noted that the uric acid reached 10.5 mg and the urea 55 mg per 100 c c of blood, although the creatinin figure was quite normal

The results collected in Table 3 summarize observations illustrative of those on which our views on this subject have been based Typical cases of gout show, as a rule, blood uric acid values from two to five times the normal (Group I) The amounts of urea and creatinin are normal, or in the case of urea only slightly above normal Many early cases of nephritis, probably of the interstitial type, give blood pictures which differ little from those of gout<sup>25</sup> (Group II) The uric acid findings are quite as high and the urea content varies from only slightly above to more than double the normal amount The creatinin is only slightly increased As the condition of the cases of this type becomes more severe, the retention of urea increases, until we have high values for urea as well as for uric acid (Group III) If improvement takes place, the concentration of urea gradually falls until the picture is that of the preceding group If, on the other hand, the case goes on to a fatal termination, the retention of uric acid and urea is followed by that of creatinin, the concentration of which may reach twenty times the normal (Group IV)

#### SUMMARY

A series of thirty cases are recorded with high values for the uric acid of the blood, but without a corresponding retention of urea and creatinin These cases were apparently suffering from "early interstitial nephritis," probably secondary in many instances to other systemic disturbances Since the blood urea was not markedly increased or the phthalein output markedly decreased (in certain cases), it is believed that the uric acid was of considerable value as an early diagnostic test The possibility is further suggested that a retention of uric acid may be earlier evidence of renal impairment of an interstitial type than the classical tests of albuminuria and cylinduria

The blood pictures in early interstitial nephritis and gout are strikingly similar, particularly as regards the increase in uric acid In view of the other clinical signs in common, it would seem that this similarity must be more than accidental

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24 Some of these cases have already received attention in another connection (blood sugar), Cf Myers, V C, and Bailey, C V Jour Biol Chem, 1916, *xxiv*, 147

25 The relation of uric acid to gout will be made the topic of a future communication from this laboratory by one of us (M S F) and Dr C V Bailey

From the data in Table 3 it is evident that as the permeability of the kidney is lowered in the type of cases studied, it becomes apparent, first, by a retention of uric acid, later by that of urea, and lastly, by creatinin, producing a "staircase effect"

# THE EFFECTS OF SUPRARENAL FEEDING \*

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Within recent years several careful studies have been made of the effects of feeding different ductless gland substances. So far as we are aware, however, the suprarenal has received little attention. The matter seemed worthy of investigation for two reasons. Suprarenal gland substance is still on trial in practical therapeutics. Although many observers have been unable to detect in it significant therapeutic virtues, others claim more fortunate results. Williams,<sup>1</sup> for example, values it highly in the treatment of so-called neurasthema, which he maintains is frequently a form of adrenal deficiency. In a case of impotency in the male, Belfield<sup>2</sup> has reported striking improvement following the use of desiccated suprarenal substance. It seemed desirable, therefore, to see if any definite objective evidence could be obtained that suprarenal substance when given by mouth has any specific effect in the body.

As further basis for the research there is on record some rather convincing evidence of a specific relationship between the suprarenal cortex and the sex glands. This evidence has recently been reviewed thoroughly by Glynn.<sup>3</sup> More recently McAuliff<sup>4</sup> has also briefly considered it.

That there is a relation between the adrenals and the sex glands was postulated by Meckel<sup>5</sup> as early as 1806. His conclusion was based on personal observations that in certain aborted fetuses both adrenals and gonads were lacking, in animals such as the guinea-pig, in which reproductive proclivities are marked, the adrenals are relatively large, in many animals the gonads and adrenals are closely associated in position, and in several cases of diseases of the genitalia adrenal degen-

\* Submitted for publication Feb 17, 1916

\* From the Laboratory of Physiology, Northwestern University Medical School

1 Williams, T A. The Syndrome of Adrenal Insufficiency, Jour Am Med Assn, 1914, lxiii, 2203

2 Belfield, W T. Some Causes of Sterility and Impotence in the Male, *Ibid*, 1912, lix, 1420

3 Glynn, Quart Jour Med, 1912, v, 157

4 McAuliff, G R. Hypertrichosis, Variations in Female Secondary Sexual Characteristics, and Internal Secretions, Jour Am Med Assn, 1916, lxxvi, 15

5 Meckel. Cited by Nagle, Note 6

eration occurred. Meckel's evidence has since been controverted by various writers, notably by Nagle<sup>6</sup> in 1836, but the idea has persisted. Von Neugebauer<sup>7</sup> in 1908 was able to find in the literature thirteen cases in which hermaphroditism was associated with marked hypertrophy of the adrenals. Bullock and Sequeira<sup>8</sup> collected reports of twelve children showing sexual precocity who at necropsy proved to have enlarged adrenals. Various other instances of an association of sex anomalies with adrenal hypertrophy are on record.<sup>4</sup> The relation of suprarenal *deficiency* to the reproductive function seems to have received little attention. One of us, however, has observed a diminution in the number of offspring from female guinea-pigs deprived of one adrenal,<sup>9</sup> although the animals appeared to be perfectly normal otherwise.

The experiments on which this paper is based were made on white rats. The series comprises forty-eight experimental and twenty-five control animals. White rats were selected as subjects because of the ease with which they can be obtained and reared under laboratory conditions, and because the anatomical features of these animals have already been elaborately studied.<sup>10</sup> It was hoped that by duplicating the environmental conditions maintained by previous observers we should be able to use their results as a basis of comparison and escape the necessity of working out separate controls for our own series. This plan, however, proved impracticable. A preliminary investigation showed that our normal animals varied widely from the established "standards."

#### METHOD OF PROCEDURE

The following procedures were employed. The rats were bred in the laboratory. Of each litter one to three individuals were selected as controls and the others were put in the experimental series. They were weaned at the age of 16 to 24 days, and one to three days later the experimental feeding began. All members of the litter received the same treatment throughout, except that the experimental animals received desiccated suprarenal gland. (The commercial product of Parke, Davis & Co. was used.) It was first necessary to determine the proper dosage. The plan was to use as much as feasible. It was found, however, that the rats at first could not safely be given more than  $\frac{1}{4}$  grain. This they received in the morning before being fed. The material was secured in 1 grain tablets. These were soaked in water until dissolved, then mixed with bread and milk. The members of each litter received their quota together. The food was scattered so that each got its proper share. It was eaten eagerly. As the animals grew older the size of the dose was increased, so that by the time the rat reached a weight of 100 gm. it was receiving from 1 to 2 grains. The material was administered once a day, six days a week. The experimental

6 Nagle. Muller's Arch, 1836, p. 365.

7 Von Neugebauer. Hermaphroditismus beim Menschen, Leipzig, 1908, p. 688.

8 Bullock and Sequeira. Trans. Path. Soc., London, 1905, lv, 189.

9 Hoskins, R. G. Am. Jour. Med. Sc., 1911, cxli, 374, 535.

10 Donaldson. The Rat, Memoirs Wistar Inst. No. 6, Philadelphia, 1915.

period varied from two to eight weeks. The feeding continued in each case up to the time of sacrificing the animal.

Since the animals were to be killed before the breeding age, the sexes were not segregated. In case of none of the animals was copulation observed, nor did any pregnancy occur. They were fed cracked corn and bread and whole milk. The corn was kept constantly before them and they received all the bread and milk they would eat once a day. In some cases the control animals received enough dried blood to compensate for the protein of the suprarenal substance fed. In other instances this was omitted. In view of the fact that each rat was on full milk diet, the food value of the small quantity of desiccated gland was deemed negligible.

At various ages from 5 to 12 weeks the animals were killed. They were weighed in the morning before receiving the bread and milk. Then, having been chloroformed, each was bled to death from the aorta or heart. The following glands were at once removed and weighed: Hypophysis, thyroid, thymus, heart, suprarenals, spleen, kidneys and ovaries or testes (freed from epididymus). Each organ was carefully freed from adventitious tissues and rinsed in Ringer's solution. It was then dried on filter paper and quickly weighed on a delicate balance. The hypophysis and ovaries were weighed to tenths of a milligram and the other organs to milligrams or centigrams, depending on the size. For details as to securing the different organs the reader is referred to Jackson's descriptions.<sup>11</sup> The smaller organs can best be isolated by dissecting them out freely and transferring to a piece of smooth cork. The organs are rolled about the adventitious tags of tissue which adhere somewhat to the cork can be trimmed off with a sharp scalpel. A dissecting microscope is needed at first, but with practice this can be dispensed with.

The data secured were studied as follows. The organ weights were first reduced to percentages of body weights. These percentage weights were then transferred to coordinate paper, using the percentage weights as ordinates and the body weights as abscissae. A homogeneous distribution of the dots representing experimental and control weights was interpreted as showing that the suprarenal feeding had had no significant effect on the growth of the gland in question. This in turn was taken to indicate that no significant influence on the gland function had been exerted. A segregation of dots, on the other hand, indicated a corresponding influence on the gland. The thymus gland is supposed to vary according to age rather than to body weight. We plotted the percentage weight of this organ, therefore, against both body weight and age.

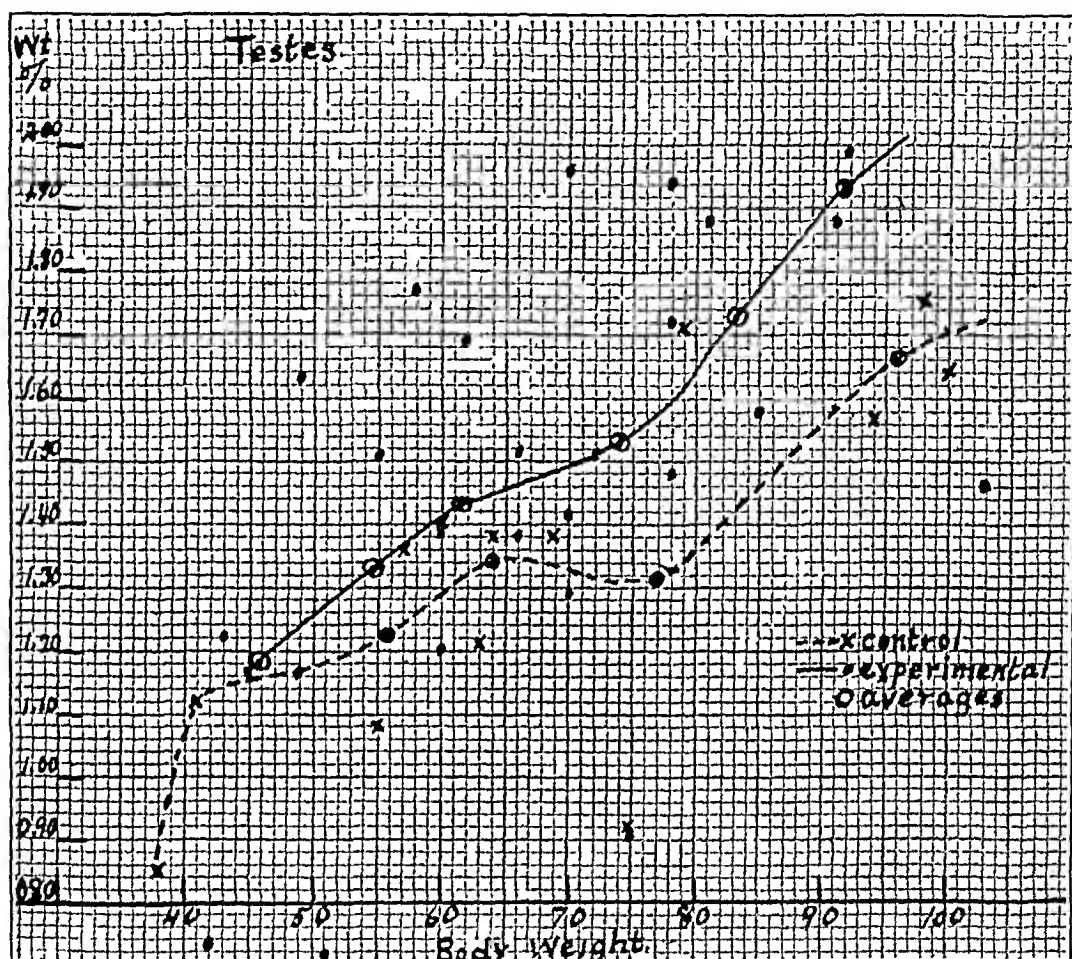
## RESULTS

In case of most of the organs, no consistent deviations from the normal could be detected. The relatively small number of animals used as compared with the variability encountered would not permit the recognition of smaller deviations, even though these were characteristic. Our negative results are therefore not conclusive. As regards the pituitary, and, in case of the smaller animals, the ovaries, our method of weighing seemed inadequate. Evaporation might easily have introduced significant errors. The spleens of the experimental series averaged somewhat smaller than those of the controls, but the spleen is an unusually variable structure. This result, therefore, is only suggestive. The ovaries of the sixteen experimental animals were larger

<sup>11</sup> Jackson. *Am Jour Anat*, 1913, xv, 1

than those of eight controls, but these numbers are too small to mean much. They justify further study, however.

In case of the testes, a rather consistent hypertrophy was observed. The chart is reproduced in the accompanying figure. The table includes the data on which the chart is based. Even disregarding the extreme cases, which are of questionable significance, the average of the experimental animals is materially higher than that of the controls. This series comprised twenty-six and thirteen animals, respectively.



Weight of testes of thirteen normal rats and twenty-six rats fed with desiccated suprarenal gland. Ordinates=gland weights expressed as percentages of body weight, abscissae=body weight.

The influence of the suprarenal feeding on body growth was also considered. There was no difference that could be detected. There is much variability in growth, however, even within a given litter kept under identical conditions, and this would render the detection of slight differences impossible in a series of this magnitude.

The study is obviously incomplete. It is regarded as merely a preliminary investigation. It should be extended to include a larger number of individuals and different species. Careful cytological study should be made of the testes to see whether the spermatogenic or the interstitial tissue is affected, or if both share in the hypertrophy. Cor-

related with this, an investigation should be made of the effects of supra-renal feeding on the development of the sex characteristics. For such a study some animal, such as the chick, with well-marked second-

TABLE OF WEIGHTS EXPRESSED AS PERCENTAGES OF BODY WEIGHT OF TESTES OF  
NORMAL AND EXPERIMENTAL WHITE RATS AT VARIOUS AGES,  
THE LATTER HAD DISSECTED SUPRARENAL GLAND

Experimental				Control		
Body Weight, Gm	Age, Days	Days Fed	Testes Weight, Per Cent	Body Weight, Gm	Age, Fed	Testes Weight, Per Cent
				38	30	0.85
42	31	14	0.73			
43	63	11	1.21			
15	39	17	1.16			
49	56	34	1.63			
49	43	21	1.17	41	56	1.12
Av 45.6	46.4	25.4	1.18	41	56	1.12
51	63	46	0.71			
55	43	21	1.51	55	39	1.03
58	43	21	1.77	57	43	1.36
Av 54.7	51	29	1.33	56	41	1.22
60	41	10	1.20			
60	43	24	1.39	60	82	1.40
62	43	24	1.69	63	43	1.21
66	64	39	1.51	64	43	1.38
66	42	20	1.98	69	41	1.38
Av 62.8	46.6	25.2	1.43	64	52	1.34
70	43	24	1.29			
70	64	39	1.42			
70	63	46	1.96			
72	65	43	1.51			
75	65	42	0.91			
78	82	56	1.48	75	81	0.92
78	82	57	1.72	79	64	1.71
78	61	34	1.94			
Av 74	66.2	42.6	1.53	77	72.5	1.32
81	81	55	1.88			
85	82	56	1.58			
Av 83	81.5	55.5	1.73			
91	78	57	1.88	94	79	1.57
92	66	39	1.99	98	86	1.75
Av 91.5	73	48	1.93	96	82.5	1.66
103	79	56	1.46	100	66	1.64

dary sex characteristics, might be more satisfactory than the rat. As one phase of such a study the age at which breeding begins should be considered. These points we hope to investigate later.

The question arises To what constituent of the gland material is the testicular hypertrophy due? In the clinical reports of suprarenal hypertrophy associated with sex anomalies the cortex of the gland mainly is affected The amount of medullary material, namely, adrenin, in the small quantity of gland substance fed, was of course minute Moreover, absorption of adrenin from the gastro-intestinal tract occurs only to a slight extent before the material is destroyed It is altogether likely, therefore, that the hypertrophy observed is to be ascribed to the cortex portion

Possibly the results secured would justify further attention to the therapeutic possibilities of desiccated suprarenal in cases of infantilism or sexual impotency Often more than one of the endocrinous glands are involved, and in such cases no one gland substance could be expected to restore the balance In cases, however, in which the fault lies primarily with the suprarenals, such medication might be effective

#### SUMMARY AND CONCLUSIONS

Forty-five white rats were fed desiccated suprarenal for varying periods from two to nine weeks Twenty-six animals from the same litters were kept as controls The rate of growth and the weights of various glands were determined in each series No differences in the two series could be detected in kidneys, heart, hypophysis, thyroid, thymus or suprarenals The spleens of the experimental series were somewhat smaller than those of the controls, but highly variable The ovaries in the few cases studied were larger in the experimental series The testes (twenty-six experimental, thirteen control) showed hypertrophy These results in confirmation of clinical evidence indicate that the suprarenals exert a stimulating effect on the testes

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## BOOK REVIEW

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**PATHOGENIC MICRO-ORGANISMS** (Including Bacteria and Protozoa) A Practical Manual for Students, Physicians and Health Officers By WILLIAM H PARK, M D, Professor of Bacteriology and Hygiene in the University and Bellevue Hospital Medical College, and Director of the Bureau of Laboratories of the Department of Health, New York City, and ANNA W WILLIAMS, M D, Assistant Director of the Bureau of Laboratories, New York City, Consulting Pathologist to the New York Infirmary for Women and Children New (5th) edition, thoroughly revised Octavo, 684 pages, with 210 illustrations and 9 full-page plates Cloth, \$4.00, net Lea & Febiger, Publishers, Philadelphia and New York, 1914

The fifth edition of this authoritative work is well adapted to continue its popularity. It has been revised thoroughly, new material has been added in many places, and some rearrangements have been made that improve its order and add to the ease of reference. As an example of completeness of revision may be mentioned the description of the Schick reaction for the detection of immunity in diphtheria, and its technique. The account of the bacteriology of pneumonia is also as near the times as possible. At the same time, the rapidity of progress in bacteriology is illustrated by the fact that the important work on *Meningitis* by Ashford and others appeared after the publication, while most of the work on the endamebias of the mouth was too recent to be included. In the discussion of streptococci, which is very good, more could have been said of septic endocarditis. There are reasons for thinking many practicing physicians do not keep as well informed on all the phases of microbiology as they should. For these, original articles are too numerous and too hard to understand. This work, by reason of its concise and yet lively style, and the unusual experience of its authors as investigators as well as clinical and public health experts, can be consulted with satisfaction by all classes of readers—beginners in bacteriology, professionals in boards of health, and practitioners of medicine in all its branches, and in all degrees of bacteriologic preparedness or unpreparedness.

The mechanical execution of the book is good on the whole, but many of the halftone and color illustrations are sadly inferior. The bibliographic references are well selected, but the spelling of proper names has suffered rather more than it should. It is to be hoped the work will continue to receive revision and retain its well earned reputation.

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## MULTIPLE ABSCESES OF THE BRAIN IN INFANCY<sup>1</sup>

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During the past year the following case, that proved to be multiple abscesses of the brain, and that, clinically, was practically undifferentiable from chronic internal hydrocephalus, came under observation. Certain unusual features make it worthy of reporting. The clinical history of the case was as follows:

### REPORT OF CASE

*History*—T. D., a white male infant, aged 23 months, was brought to the Harriet Lane Home in the service of Dr. John Howland, Oct. 27, 1914, with the complaint "Large Head." The change had been first noticed when the child was 18 months old.

*Family History*—Father and mother living and well at 46 and 23 years respectively, two other children, aged 5 and 3, living and well, no history of miscarriages, or of tuberculosis.

*Previous History*—Full term, noninstrumental birth. Pregnancy, the third, labor rather hard (pains being present for two days before the child was born). Infant apparently normal and healthy. Weight about 9 pounds.

The child was breast fed for two months, and then given diluted cow's milk with sugar. He always took his food well. Other articles were added to his diet at 15 months.

He cut his teeth at 5 months, sat up at 6 months, and walked and said a few words at 15 months. He had a severe attack of pertussis at 7 months, apparently without after effects. There had never been any evidence of middle ear affection.

He stopped walking and talking at 16 months, and two months later it was noticed that his head was enlarged. During the six weeks preceding admission, the head was said to have increased a good deal in size. The child had never had convulsions. There was no history of injury or trauma.

*Examination*—The child was admitted to the hospital October 27 as a well-nourished, well-developed boy, 74 cm. in length, inattentive and with an expressionless face. He closed his eyes or turned away his head if light was flashed in his face and did not grasp objects. His head was large, the circumference 52 cm. It was much wider through the parietal diameter than through the frontal diameter, so that viewed from above, it was rather triangular in shape, with the apex at the forehead. The forehead bulged, giving the impression that the eyes were sunken. The anterior fontanel measured 3 x 3 cm., and was situated further back than normal. It was tense, but not

<sup>1</sup> Submitted for publication Jan. 12, 1916.

\* From the Department of Pathology of the Johns Hopkins Hospital and University.



Fig 1—Sagittal section of brain showing abscess Two-thirds natural size, section taken from 1

bulging, pulsation was transmitted. The sagittal suture was ununited and moveable, becoming soft and yielding at the posterior fontanel. The other sutures were firmly united. The superficial veins, particularly over the frontal and lateral regions of the skull, were prominent. The eyes appeared deeply placed, but were not dislocated downward, followed objects well. There was no nystagmus or paralysis. The chest was normal in form, its circumference 47 cm. The heart, lungs and abdomen seemed normal.

On further examination, it was seen that the child grasped objects fairly well with his left hand, but refused to take them with his right hand. If the left arm was held, the child moved the right arm poorly and was not able to eat with it. He took bread well with his left hand, but there was marked tremor as he moved it to his mouth. The difference in the movements of the two hands was quite marked. When the child desired to be taken up, he stretched out his left hand, the right remained still, or, at least, was moved less freely.



Fig 2—Transverse section immediately in front of tips of temporal lobes. Photograph  $\frac{2}{3}$  natural size. Shows displacement of right lateral ventricle and distortion of other structures, also relative enlargement of left hemisphere.

The reflexes in both arms and the knee jerks were exaggerated and equal. The cremasteric reflexes were present. There was no spasticity in the arms or the legs. There were no contractures. The Babinski was negative. A fairly sustained ankle clonus was obtained at times. The child did not speak but seemed to understand what was said to him. Sensation was present and equal on the two sides, so far as could be determined.

Temperature, on admission, 99 F, pulse, 140 to 160, respiration, 28, white count, 10,000, urinary examination, negative, Roentgen-ray report as follows: "Head markedly deformed, external hydrocephalus—sella shows evidence of pressure." Lumbar puncture yielded 25 cc of clear fluid apparently under increased pressure—(pressure on the anterior fontanel was thought to increase the rate of flow)—and containing 7 lymphocytes and many red blood cells per

cubic centimeter, globulin test positive. The Wassermann test (blood and spinal fluid) was negative. The von Pirquet test was negative.

*Operation*—Two ventricular punctures were made about six days apart (Dr Dandy). Attempts to enter the left ventricle and the third ventricle were unsuccessful. Puncture of the right ventricle yielded a few drops of blood, tinged, it was thought, with cerebrospinal fluid and followed by freely flowing, dark, red blood. A sense of increased resistance felt on the right side suggested the presence of brain tumor. It was not felt that the ventricles were dilated.

A second lumbar puncture (November 5) yielded 10 c.c. of fluid with 35 cells per c.mm. A positive globulin test was obtained.

The phenolphthalein test done at this time showed an excretion within normal limits.<sup>1</sup>



Fig 3—Transverse section half way between tips of temporal lobes and anterior border of pons. Photograph  $\frac{1}{2}$  natural size. Shows displaced ventricles and median structures, large size of left hemisphere, and beginning of abscess cavity.

The condition of the child remained unchanged. The temperature remained normal. The white count remained low. There was no perceptible increase in the size of head after admission.

*Exploratory Craniotomy*—(Dr Heuer). The skull was thin, the dura was not adherent. A needle was inserted into the frontal area, which appeared relatively softer, a little fluid escaped from the path left after withdrawing the needle. It was apparently under no pressure. The opening was enlarged by blunt dissection until a good exposure of the ventricle (right lateral) was obtained. The ventricle appeared to be definitely enlarged (diameter 7.5 cm.)

<sup>1</sup> Dandy, Walter E., and Blackfan, Kenneth, D. Internal Hydrocephalus, An Experimental, Clinical and Pathological Study, *Am Jour Dis Child*, 1914, viii, 406.

and could be followed practically to the posterior limit, and also anteriorly for quite a distance. On vacating the field opening on the cortex closed over through sagging, "drooping," in of its walls due to release of the fluid tension within. The membranes and bone flap were closed as usual.

*Postoperative Course*—Following the operation, the child was not able to use either the left arm or leg, and by the third night, these had both become spastic. The temperature remained elevated, 104 to 106, the pulse was rapid. The child was often restless and often made purposeless movements. His eyes deviated to the left. Edema of the *right* eye appeared on the fifteenth day and became marked, on the sixteenth day the child was unable to close his *left* eye. The leukocytes at this time reached 22,600. Jerky movements appeared in the right arm and leg. The temperature rose to 106.5 at midnight of the sixteenth, and the child died at 4 15 a. m., November 17.



Fig 4—Transverse section immediately in front of pons. Photograph,  $\frac{1}{2}$  natural size. Showing operative wound, large right lateral ventricle, obliterated left lateral ventricle, large abscess cavity with thick pyogenic membrane. A second section half way to the tip of the posterior lobe is seen to pass through the posterior wall of the cavity, and the median wall of the cavity is seen to bulge laterally (due to pressure of a second abscess).

*Postmortem Examination (Nine Hours After Death)*<sup>2</sup>—When the dura was opened it was seen that the left hemisphere was distinctly larger than the right. The convolutions on the left side were wide and flat. The left occipital lobe was softer than the other portions of the brain, and the dura was slightly adherent at this point. Sections were made of the brain. On transverse section of the hemispheres at the tips of the temporal lobes (Fig 2), the right ventricle was seen cut across, the left ventricle was not visible.

<sup>2</sup> Permission was granted for examination of the brain only.

Section through the temporal lobes at the level of the optic chiasm and parallel to the first section, revealed a *large abscess* in the white matter of the left hemisphere, the anterior wall of the abscess reaching just to the section (Figs 2 and 3) The left ventricle was seen pushed over toward the right and collapsed The right ventricle appeared a little larger than normal, but its increase in size was not very marked

A section at the level of the anterior border of the pons (Fig 4) showed that the abscess involved much of the hemisphere It measured 62 x 5 cm in the transverse and vertical directions, respectively, and 75 cm in the antero-posterior direction It was definitely encapsulated, and contained greenish-yellow, purulent material of creamy consistency, homogeneous and not tenacious The wall of the cavity was firm, apparently composed of dense connective tissue and 3 mm in thickness The left ventricle appeared somewhat distended

The aqueduct of Sylvius had been much dislodged toward the right There was evidently no communication between the left ventricle, which was collapsed, from direct pressure of the abscess, and the right ventricle,



Fig 5—Transverse section half way between plane of Figure 4 and the tip of the occipital lobe, showing second large abscess Photograph,  $\frac{2}{3}$  natural size

which was perhaps a little distended The obstruction of the aqueduct of Sylvius might well have caused an internal hydrocephalus

The conditions found on the right side appeared to be solely those of displacement caused by pressure from the large abscess

After the pus had been evacuated from the posterior half of the abscess cavity, it was seen that the posterior median wall bulged laterally as a fluctuating tumor A third section, half-way between the anterior border of the pons and the tip of the occipital lobe and in a plane parallel to those of the previous sections, passed through the posterior portion of the first abscess and diametrically across a smaller one (Fig 5) This somewhat smaller abscess lay thus mesial to the posterior extremity of the first abscess and projected backward and outward into the occipital lobe The collapsed condition of the lateral ventricle is well seen in the photograph

A fourth section made in the same manner as the third, revealed three smaller abscesses in the tips of the occipital lobe (Figs 4, 5 and 6) The smaller of these had much less definitely organized walls and the distinction between wall and puriform contents was not so well defined,

## JAMES B HOLMES

Preparations from the contents of the larger cavities and from the walls showed no micro-organisms, "acid-fast" or other, nor were any found in the sediment after digestion in a strongly alkaline solution of sodium hypochlorite (antiformin). Cultures were not made owing to the body having been injected with solution of formaldehyd

*Microscopical Notes*—Sections extending through the wall of the cavity and the adjacent brain tissue and taken from a variety of locations all showed essentially the same structure. That taken from the area marked "x" in Figure 1 forms the basis of the following description. As is seen in the figure, the section extends from the inner surface of the dense fibrous wall of the cavity, through it and the compressed brain tissue to the pia. The relations are well shown in the colored drawing made by Mr Broedel from the microscopical preparation (Fig 7). In the photograph, a cortical fissure is seen traversing the section. It is displaced by the tumor until it runs almost parallel to the wall of the cavity. In the microscopical preparation, this appears at c', where a portion of the pia and its vessels is seen lying between areas of compressed cortex.

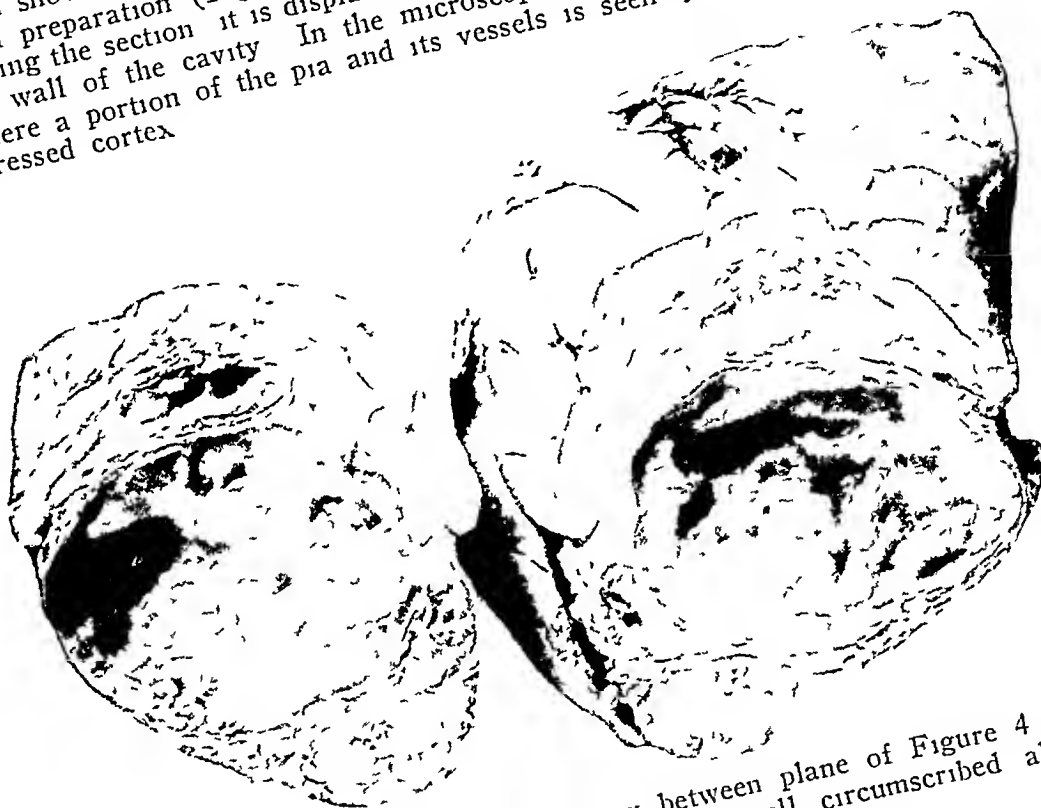


Fig 6—Transverse section half way between plane of Figure 4 and tip of occipital lobe, showing smaller and less well circumscribed abscesses. Photograph, about  $\frac{2}{3}$  natural size

For convenience of description, the section may be divided into layers, or regions.

The cellular exudate (a) or puriform contents of the cavity is seen to consist of mononuclear cells, accompanied by very few polymorphonuclear cells. Many of the mononuclear cells contain globules of lipid substance that have been more or less deeply stained with sudan III.

The polymorphonuclear cells are few in number, they are typical pus cells in the amount of stainable lipid substance that they contain, and in the depth of staining of the nucleus. The nuclei are usually round or ovoid in shape and contain a centrally placed nucleolus and chromatin granules scattered toward the periphery. Some of the nuclei are much more deeply stained than others and in them the arrangement of the chromatin is less evident. Where the accumulation of the lipid substance is great the nucleus is dis-



placed toward the side of the cell, it may even come to lie on the periphery of a large globule of fat. These nuclei are, in no case, polymorphous (for example, clover-leaf), in form, and the occasional pus cells found seem to be free from the stainable lipoids. Certain ones of the larger fat-containing cells have multiple nuclei, these nuclei resemble the single nuclei.

These large mononuclear cells containing fatty substances and staining more or less deeply with sudan III, are found here and there throughout the section. They appear to be unusually good examples of the phagocytic cells of the central nervous system, the so-called *cerebral granule cells*. They form the most conspicuous and interesting feature of the sections in this case. Their origin will be discussed hereafter.

The wall of the cavity, (b), is formed of dense fibrous tissue. The characteristic cells are long and slender, are tangentially disposed, and intertwine, more or less, with their fellows. The protoplasm has a uniform glassy appearance or is finely granular, and is free from fatty particles. The nuclei are slender, tapering, and closely resemble the nuclei of ordinary connective tissue in form and arrangement of chromatin. In some places small groups of cells are seen to be included in the fibrous wall, these are, in every way, the counterparts of the mononuclear cells composing the exudate described above. The fibrous capsule, as a whole, is conspicuously free from capillaries or cellular inclusions, and appears as a dense membrane composed of long fusiform cells, with infrequent, slender nuclei. Cells like those seen in the exudate occur, however, scattered here and there through this area. Many of the more centrally placed ones stain faintly with sudan III, but as the margins are approached, these myelin-bearing cells become more numerous, and larger, and more deeply staining. The nuclei may become larger, less regular, darker and more diffusely staining.

At the junction of the fibrous layer and the layer of exudate, two distinct types of cells are seen. The first is the typical cell of the exudate, a round or ovoid cell with a round nucleus in which there is a more or less centrally placed nucleolus and peripherally small globular masses of chromatin. When laden with myelin, the appearance of these cells is modified in the manner described above. The second type of cell occurs in much smaller numbers. It has a round, ovoid or elongated, nucleus, several times larger than that of the cell last mentioned, and vesicular in character, with the chromatin scattered rather evenly throughout the nucleus in the form of fine granules. These cells are seen most frequently in close proximity to the delicate capillary processes and appear to be endothelial polyblasts. Every transition between these and the characteristic cells of the fibrous capsule appears to be present. The nuclei of the fat-containing cells are rarely, if ever, found to resemble the nuclei of these cells.

Adjacent to the fibrous capsule and blending with it is a zone of blood vessels (c). These are relatively numerous and large. Branches from them penetrate the fibrous capsule here and there and may be found extending quite to the cellular exudate on the opposite surface. Lymphatic spaces, (d), are seen near the larger vessels. Near some of them are seen also, collections of small round cells. The cells forming these collections are quite distinct from the mononuclear cells forming the exudate described above. Transitional forms are not clearly distinguished.

The figures seen at (c) are small areas of brain tissue much infiltrated with cells and more or less isolated by connective tissue growth. They come thus to resemble "cell nests." The infiltrating cells have irregular, somewhat vesicular nuclei, bearing scattered masses of chromatin of varying sizes, and with, or without, a definite nucleolus. In some of these areas a diffuse reddish staining indicates the presence of minute globules of liquid substances in the degenerating tissue, these globules are here seldom phagocytosed.



Fig 7—Color plate showing microscopic details For full explanation see text



The zone marked (e) is a layer of cerebral tissue that has been compressed and, in a large measure, absorbed. It resembles closely the neighboring area, (e'), and a description of the latter will serve for both. The two areas are separated by an infolding of the pia and its vessels (c'). The figures described under (c) are here seen again.

The zone (e') is composed in the main of much compressed and degenerated medullary matter. The tissue has a tendency to fall into strands that represent axis cylinders or groups of them, and are tangentially disposed. Fine droplets of lipid substance stained with sudan III are seen everywhere. Here and there larger aggregates are seen, these are often phagocytosed. Large, fat-containing cells become progressively more numerous as the zone (c') is approached. The total number of cells in the zone is relatively much increased. Of these cells, two types may be recognized: (1) a cell with a large, clear vesicular nucleus, with one or more larger masses of chromatin (nucleoli) and a reticulated appearance, and (2) a cell with a much smaller round nucleus varying much in depth of staining. It is these latter cells that contain phagocytosed myelin droplets. The depth of staining of the nucleus here, again, is often proportionate to the amount of phagocytosed myelin within the cell. The cells are rather readily classified into these two types, though occasional cells are seen that are intermediate in appearance.

The capillaries in this zone are relatively numerous. This is, in a measure, due to the absorption of degenerated cerebral tissue and the consequent approximation of previously existing capillaries. These vessels are nowhere occluded, there is no accumulation of infiltrating cells in their neighborhood, and no proliferation of the cells in their walls is seen. The endothelial cells in their walls are usually readily distinguishable from the cells of either of the above mentioned groups. Heavily laden "granule cells" are occasionally seen in close proximity to the walls of the capillaries. In some places, fine myelin droplets are seen also in the walls of the capillaries. Usually, they appear free, but sometimes they seem to have been phagocytosed by cells within the capillary walls.

In the most superficial zone (g) the number of cells is relatively much less. There is noticeable absence of the minute stained myelin droplets elsewhere seen lying free in the degenerating cerebral tissue, and there appears to be much less injury to the brain substance. The large ganglion cells, however, are usually not well preserved and are infrequently met. Cells of the first type described in zone (e') are the prevailing cells. The stainable lipid substances are here present almost exclusively in cells of the second type, and give the body of these cells a faint reddish-yellow tinge, or, where most abundant, completely fill it with a more or less globular mass that stains deeply with sudan III. Many of these smaller cells are seen without such stainable substances in the cell body or in the immediate neighborhood, they have the appearance of the cells of the second type as prescribed in zone (e'). The nucleus in those containing little myelin is often unchanged, as the amount of substance increases the nucleus tends to become more and more diffusely staining and irregular in outline, it may become quite pyknotic.

Finally, the section terminates in a border of thickened pia (h). Its capillaries are somewhat enlarged. Polymorphs are not observed. There is no obvious cellular infiltration. Immediately under the pia is a narrow, incomplete layer in which degeneration appears to be more active than further in, and unphagocytosed myelin droplets of small size are seen.

Taken as a whole, the section is conspicuous in the unusual development and sharp definition of the fibrous capsule, or zone of connective tissue reaction, and in the prominence and great variety of the "cerebral granule cells," of "Gluge's corpuscles."<sup>3</sup>

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3 Gluge, Gottlieb. *Abhandl. f. Physiol. u. Pathol.*, Jena, 1841, pp. 30 and 35, and Plate I.

## DISCUSSION

Neither the clinical history nor the necropsy findings, gross and microscopical, throw any certain light on the etiology of the condition found postmortem. It is necessary to fall back in part on a consideration of the etiological possibilities. Of these, three stand out prominently, and may be taken up in inverse order of probability: glioma, solitary tubercle and pyogenic abscess. A fourth and more remote possibility may be mentioned in passing—cerebral cysts.

Cerebral cysts in children may be the result of one of several conditions. Necrotic cysts may replace areas of softening. Cyst formation may follow hemorrhage<sup>4</sup>—porencephalic cysts are probably to be included here. Cysts appear also in connection with gliomas. Those due to cysticercus and echinococcus do not appear to have been observed in children, their contents are also distinctive.

The content of such cysts is usually a clear or milky fluid, the opaqueness being due to the presence of numerous fat-containing cells (Ziehen)<sup>5</sup>. No reference is found to the appearance of puriform contents unless infection has occurred. The wall of the cyst may or may not be pigmented.

That such a condition was here present seems a most remote possibility.

*Glioma*—After solitary tubercles, gliomas are the most common cerebral tumors of childhood. They, too, may form cystic cavities containing puriform material (Ziegler)<sup>6</sup>. They may be highly vascular. Where hemorrhage or softening occurs, there appears, says Ziegler, a cavity filled with cloudy white or brown, more or less liquefied masses. Sometimes the glioma tissue forms the wall of a cyst which contains clear serum. The literature at hand does not show how frequently the condition may simulate abscess.

*Solitary Tubercles*—These are, in comparison with abscess, very common in childhood. Tuberculous tumors are the most frequent form of intracranial neoplasm in childhood, over 50 per cent of all brain

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4 In adults, the tissue adjacent to an area of hemorrhage responds in the course of two months with the formation of a capsule composed partly of connective tissue derived from the wall of the blood vessels and partly, according to Ziehen (in Bruns-Cramer-Ziehen Handbuch der Nervenkrankheiten im Kindesalter, Berlin, 1912), of glia. Gluge's cells appear in the neighborhood, the injured tissue undergoes colliquative necrosis (Ziegler Lehrbuch der pathologische Anatomie, Jena, 1906) and is removed or absorbed, the color of the contents passes gradually through browns into yellows, and ultimately becomes milky or quite clear. This last is, as a rule, the definitive condition in children (Ziehen) though in adults scar formation seems to be more common.

5 Ziehen. In Bruns-Cramer-Ziehen Handbuch der Nervenkrankheiten im Kindesalter, Berlin, 1912.

6 Ziegler Lehrbuch der Pathologische Anatomie, Jena, 1906.

growths in childhood are of this type (Starr).<sup>7</sup> They sometimes suppurate and break down and may then simulate simple abscess. Ziegler wrote:

Not infrequently softening and liquefying processes appear in the tubercle and lead to the formation of abscess cavities filled with yellowish-white pus, or indeed with greenish-white pus.

Ziehen considered the existence of idiopathic abscesses in children highly doubtful, and mentioned solitary tubercles that have undergone suppuration as a possible explanation of some cases of so-called idiopathic abscess. In isolated cases, tubercle bacilli have been demonstrated in the wall and contents of the cavity (Fraenkel<sup>8</sup> 1887, Oppenheim<sup>9</sup> and others<sup>10</sup>) but in the main the recognition of the tuberculous origin of such abscesses must be extremely difficult.

*Pyogenic Abscess.*—Pyogenic abscesses of the brain are quite rare in children. They are decidedly rarer than solitary tubercles and other tumors and are exceptionally rare under 5 years of age. In a collection of 223 cases of cerebral abscess Gowers found 10.7 per cent. occurred in patients under 10 years of age. Okada,<sup>11</sup> in 141 cases of cerebral abscess, found 11.6 per cent. occurred in the first decade and 38.3 and 30.8 per cent. respectively, in the next two decades.

7 Starr: Organic and Functional Nervous Diseases New York and Philadelphia 1913 Ed. 4.

8. Fraenkel A: Ueber den tuberculösen Hirnabscess Deutsch. med. Wchnschr., 1887 xiv 373. Fraenkel's case was that of a young mechanic. An abscess cavity the size of a hen's egg was found in the left hemisphere at necropsy. It possessed a firm membranous wall 2 to 3 mm in thickness. The adjacent brain tissue was soft, edematous and yellowish-white. Neither in the brain nor elsewhere in the body were any gross tubercles or caseous areas found. The content of the cavity was purulent and without caseous particles. To the naked eye it had an appearance throughout of ordinary (connective-tissue) pus homogeneous odorless somewhat thick or creamy. On microscopical examination none of the ordinary pyogenic organisms were found. Instead of these, innumerable tubercle bacilli were found both in pus and in the membranous wall of the cavity. No microscopic tubercles were present.

9. Oppenheim Lehrbuch der Nervenkrankheiten Berlin 1913.

10. Rogers frequently quoted report (Absces Cérébraux Multiple, etc., Rev. neurol., 1909 xvii 772) is of interest here. He recorded a case of multiple tuberculous abscesses in the brain of a woman of 39 in whom there were tuberculous pulmonary foci, but who came under observation because of hemiplegia. He reviewed the literature of the subject and found that the cerebral abscesses of the tuberculous contain a creamy thick pus of greenish-yellow color, in every way similar to the pus of the other abscesses. Also that the wall of the abscess shows nothing distinctive even in the cases in which acid-fast bacilli are present, the wall does not contain giant cells. He thinks the tubercle bacillus acquires under certain conditions the property of forming frankly pyogenic pus. His own case, however, showed a few diplococci in the pus.

11. Okada W: Diagnose und Chirurgie des ologenen Kleinhirnabscess. Klinische Vorträge a. d. Geb. d. Otologie u. Pharyngo-Rhinologie, Jena, 1900, p. 311.

Okada's figures also showed that cerebellar abscesses occur about one half as often as cerebral abscesses during the first ten years of life (It had previously been thought that the ratio was nearer one to four) He found two cases under 4 years of age (2 and 3 years, respectively), and four cases at 4 years of age

In contrast to the above figures, Heiman,<sup>12</sup> in 535 cases of otitic brain abscesses, found only 3, or 1 per cent, in children under 5 years of age, and but an equal number in the next decade

The two great causes of pyogenic abscess are middle-ear diseases and trauma The former is considered much the more common Hegener<sup>13</sup> found 0.5 per cent of 5,000 patients with chronic inflammation of the ear, seen at the Heidelberg clinic (1897-1906), developed abscesses of the brain Three quarters of them were cerebral abscesses Heiman collected 640 cases of otitic abscesses from the literature and found almost one quarter followed acute inflammation of the ear, and Dench<sup>14</sup> found twenty out of one hundred cases followed acute otitis

These abscesses are solitary in 80 to 85 per cent of the cases Metastatic or embolic abscesses are usually multiple and are even rarer in children than are solitary abscesses Seventy-five per cent of these solitary abscesses of childhood occur in the white matter of the hemisphere, being relatively more common in this location in children than in adults (B. Korner<sup>15</sup>) The remaining 25 per cent appear in the cerebellum

Trauma is a less frequent cause of solitary abscess, though second in importance Considering all ages, Gowers found 24 per cent were due to trauma Abscess formation may follow even simple concussion It usually occurs in the neighborhood of the injury, but may be produced by *contre-coup* These abscesses of traumatic origin are usually solitary Infection of the injured areas may occur long after the infliction of the injury, abscess appearing as a late result even ten or twenty years after the time of injury The symptoms usually appear, however, in the first two weeks

In the present case, there is a history of neither trauma nor middle-ear disease, and no findings suggestive of either were made at necropsy

Thrombosis and embolism are possible causes of cerebral softening and subsequent abscess formation in children, but need only be men-

12 Heiman Ein Fall von akutem otitischem Schläfenlappenabscess, Arch f Ohrenh, 1905, lxi

13 Hegener Labyrinthitis und Hirnabscess, Beitr z Anat u Physiol, Path u Therap d Ohres, etc, Berlin, 1909, ii, 359, Statistik der Ohreiterungen und Hirnkomplikationen, etc, Ztschr f Ohrenh, 1908, lvi 3

14 Dench, E. B. Otitic Brain Abscess, Am Jour Med Sc., 1907, New Series, cxxxiv, 692

15 Korner, B Citations from Ziehen and from Okada (see Notes 5 and 11)

tioned here Metastatic abscesses are usually multiple Thrush has been noted as a case of cerebral abscess by Wagner, Holt,<sup>16</sup> Zenker and Ribbert, Aschoff<sup>17</sup> and Ziehen.<sup>5</sup> In Wagner's case, the abscesses were multiple and the same fungus was obtained from the abscesses as from the mouth Actinomyces and streptothrix as causes of cerebral abscess do not appear to have been found in children

The pus found in pyogenic abscesses is variously described as being thick, greenish-yellow and sometimes fetid, characteristically greenish and thin, thin or cheesy, creamy or thin, grayish-red or stringy, usually acid, often green, or (from the presence of iron sulphid) blackish-green and often slimy gray, while according to Ziegler it is usually creamy, yellowish white or lightly greenish tinted<sup>18</sup>

Whatsoever their cause, solitary abscesses in children as young as this are extremely rare

*Granule Cells*—A few words may be said about the granule cells of the central nervous system, since they form such a prominent feature in this case

They were first described by Gluge<sup>3</sup> in 1841, and have long been called "Gluge's cells" They are more commonly called simply "granule cells," or "granule cells of the central nervous system" Our knowledge of them has been recently reviewed in its historical development by Ciaccio<sup>19</sup>

Their origin has been a matter of dispute almost since their discovery New methods of neurological technic and study have lent their support in turn to this view and to that, without confirming any The pictures usually seen in pathological specimens have proved too complex for unraveling, and there remains very much that is yet obscure That the granule cells are not derived from the nerve cells is certain They are derived either from the supporting cells of the central nervous system, the neuroglia, or they are derived from the mesenchymal cells that have come in with the capillaries, the adventitial cells, for example

The problem is being attacked in its simpler forms from the experimental side Tanaka<sup>20</sup> has shown recently that, in the case of small

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16 Holt The Diseases of Infancy and Childhood, New York, 1911

17 Aschoff Pathologische Anatomie, Jena, 1911

18 Where statements incorporated in the above discussion are not derived from standard textbooks, such as Adams (Adams and McCrae A Textbook of Pathology, Philadelphia and New York, 1914), Ziegler,<sup>5</sup> Aschoff,<sup>17</sup> Delafield and Prudden (Pathological Anatomy and Histology, New York, 1909), their source is indicated

19 Ciaccio, C Beitrag zur Kenntnis sogenannten Kornschenzellen des Zentralnervensystem, Ziegler's Beitr z path Anat u allg Path, 1911, 1

20 Tanaka, Takehiko Experimentelle Untersuchungen über die Herkunft der Kornschenzellen des Zentralnervensystems, etc, Ziegler's Beitr g path Anat u allg Path, 1911, 1



uninfected cortical wounds the granule cells are derived almost entirely from the preexisting glia cells, if not, indeed, entirely from them

With a *cold* glass probe, or needle, he produced aseptically slight wounds in the cortexes of a series of guinea-pigs. He found on killing the animals at intervals after operation that the polymorphonuclear cells and mononuclear cells were present in numbers only up to the fourth day, and very rarely thereafter. The polymorphonuclear cells may take up degeneration products and stain the size of true "granule cells," but they have always multiform, lobulated, nuclei, and may be excluded as a source of true granule cells. The lymphocytes are extremely few in number as compared with the granule cells, after the fourth day, and they remain small. In few cases, Tanaka saw a few granule cells of small size that were apparently derived from lymphocytes, but the nucleus of the majority of the granule cells was larger and paler and the chromatin differently disposed within it. Proliferation of the adventitial cells of the neighboring blood vessels was very infrequent and granule cells were rarely found in such close proximity as to suggest derivation from adventitial cells. Such origin cannot be excluded, but must be regarded as relatively quite unimportant. This is also true of the fixed tissue cells, the author could find no transition forms from fibroblast to "granule cells."

The great bulk of the "granule cells," according to Tanaka, are derived from the glia cells.

On the third day after injury (of the kind described) signs of mitoses and definite increase in the number of these cells may be seen. There is evidence of reaction in the enlarged nuclei and the increased protoplasm, which is laden already with a few granules of detritus. By the seventh day the increase in the glia cells is marked, and some possess several nuclei. Intermingled among the hypertrophied glia cells are true granule cells. The nuclei of these show the greatest resemblance to those of the adjacent hypertrophied glia cells, and every transition between the two types of cells may be seen.

In their development into "granule cells" the glia cells seem to become detached, says Tanaka, from their fibers and to become ameboid in character.<sup>21</sup>

The transition into granule cells occurs predominately (under the conditions of the experiment) during the first ten days. After two weeks the nuclei have already become smaller, are for the most part

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<sup>21</sup> That such independence should exist between the glia cell body and the fully formed glia fiber is compatible with the views of Weigert (*Beitr. z. Kenntnis d. n. mensch. Neuroglia*, etc., 1896), though disputed by Held (*Ueber den Bau d. Neuroglia*, etc., 1904). (Citations from Tanaka<sup>20</sup>)

angular, and stain more deeply. The cells slowly vanish in situ, or are carried off into the lymph spaces.

Tanaka saw no evidence of transformation of "granule cells" into cells of other types. Scar tissue developing from the overlying pia in time filled the defect caused by the injury in this experiment, in the deeper layers the neuroglia contributed to the scar formation.

This work is unconfirmed as yet. Ciaccio's<sup>19</sup> studies led him to quite other conclusions. He decided that stainable lipid globules may be found in (a) many degenerating cells in the central nervous system (and other tissues), and in (b) a special type of phagocytic cell, the "interstitial lipid cell." This interstitial lipid cell is derived, he says, from the mesenchyma, by way of the adventitial cells of the blood vessels near the injured area.

In the case here presented the microscopical pictures support Tanaka's view of the origin of the granule cells, rather than the older views. In the least injured tissue, for example in zone (g), the neuroglia cells are least affected, occasional well-defined granule cells are seen, and numerous less differentiated intermediate forms. There is, in this zone, no demonstrable reaction on the part of the capillaries. As the tumor is approached and the zone of greater compression and degeneration is entered (e'), the neuroglia cells, the granule cells, and the transitional cells become much more numerous. Reaction on the part of the capillaries, however, becomes apparent only later.

In view of the absence of signs of reaction on the part of the capillaries in zone (g) and in the absence of any demonstrable infiltration by cells derived from the blood stream itself, it is difficult to believe that those cells that appear to be undifferentiated neuroglia cells and similar cells containing minute globules of stainable lipoids, and finally, fully differentiated granule cells, are not all derived from preexisting cells of the central nervous system—the neuroglia. To postulate the presence of some undifferentiated mesenchymal cell, deposited in the brain tissue at some time during development and now reacting to stimulus, seems unnecessary.

#### SUMMARY

The case here reported represents a rare condition, multiple large abscesses in the hemisphere of an infant under 2 years of age.

It ran its course under the picture of chronic internal hydrocephalus.

That chronic internal hydrocephalus of the communicating type was not present was shown clinically by the phenolsulphonephthalein test.

The condition found at necropsy resembled closely that of multiple pyogenic abscesses of the left hemisphere.

It was not possible, however, wholly to exclude multiple tubercles which had undergone puriform softening.

Microscopically, the case is noteworthy in the unusual number of Gluge's corpuscles that are present, and in relation to theories of the origin of these cells

I wish to thank Dr Howland for the privilege of reporting this case, and Dr Adolph Meyer for his personal interest in the study of the brain in the Neurological Laboratory of the Henry Phipps Psychiatric Institute

Severn Apartments

# STUDIES ON THE PINEAL GLAND

## I EXPERIMENTAL OBSERVATIONS

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### INTRODUCTORY

The ancients believed that the pineal body or cornarium, as it was called, regulated the flow of vital spirits from the brain to the spinal cord, acting in this capacity in a manner similar to the pylorus of the stomach. It was assumed that it was a part of the brain, capable of movement, and stood as a guard between the third and fourth ventricles. But it is remarkable to find in the works of Galen,<sup>10</sup> whose name still clings to the neighboring veins, that he used the term "acervulus" in describing the psammona or sand bodies found in the gland, and in his works recur such illuminating statements as the following: "The pineal was devised for the same purpose as the other glands of the body." In the first place, "it is in substance glandular," and, observing that the blood supply came from the same source as that of the choroid, he felt that it must be as distinct from the brain proper as is this latter structure. Again, "if it was a small part of the cerebrum itself it would be found at times moved from its own situation by compressions," and lastly, he lays stress on the fact that it is not a part of the brain, because "it clings to it from the outside." From the second century until the time of Faivre, the Galenic ideas concerning the structure and function of this body prevailed, though, as is well known, Descartes regarded it as the seat of the soul.

The careful comparative studies of this organ by Faivre<sup>7</sup> in 1854 form the basis of all subsequent anatomical researches. For the next fifty years the investigation of the pineal was confined to its embryology, anatomy, and its pathology in relation to the few recorded clinical cases of tumor. During the last fifteen years only, have attempts been made to study the function of the gland by the use of the present-day experimental methods.

Because of our newly acquired knowledge that the pineal body undergoes a normal, physiological atrophy at the time of puberty, as well as the fact that several cases of tumor of the gland occurring before puberty have been associated with a marked precocity in the realm of both primary and secondary sexual characteristics, it would seem

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\* From the Laboratory of Surgical Research, the Harvard Medical School

plausible to assume that the gland, when physiologically active, tends to inhibit the development of the sexual function

Experimentally, this problem has been attacked in the usual two ways, namely, by extirpating the gland, and by the oral administration of its substance. As to the former method, the experiments, notably those recently carried out by Foa,<sup>10</sup> support the assumption just alluded to, he having experimentally reproduced by removal of the pineal body in chickens the syndrome termed by Sarteschi "macrogenitosomia precocæ"<sup>10</sup> Our own observations, to be recorded in this paper, also are interpreted in support of such a view. On the other hand, the feeding experiments of Dana and Berkeley,<sup>12</sup> and McCord<sup>16</sup> seem to indicate, contrary to what would be expected, that prolonged administration of the glandular substance likewise hastens rather than retards the somatic and sexual development.

It will be seen, therefore, that the subject needs further investigation, but before recording such results as have been obtained in this laboratory, some review is necessary, as much has been added to our knowledge since the resumé in 1909 by Marburg<sup>54</sup> and in 1912 by Kidd.<sup>70</sup>

#### PAST EMBRYOLOGICAL FINDINGS

Practically all recent investigators support the view that the gland is derived from a separate and distinct evagination of the roof of the third ventricle. Edinger<sup>7</sup> is apparently the first author to uphold the unpaired origin of the pineal gland, former investigators (Gaskell<sup>11</sup> and Dendy<sup>3</sup>) having brought rather meager evidence to show that the buds forming the two pineal organs in lower vertebrates were not both in the median line. Studnicka,<sup>21</sup> in his comparative embryological studies, finds that there are always two midline evaginations, the anterior becoming the pineal eye in those forms which retain this structure, and the posterior, the pineal body proper.

Marburg,<sup>54</sup> from studies of human embryological material, also believes in the development of the pineal body from a separate outgrowth, the pineal eye being no longer demonstrable in man. He gives a schematic representation of the relationships of the four evaginations of the diencephalon in the pineal region. Of these diverticula, the pineal body proper is concerned only with the most posterior, while the others, in the lower vertebrates, develop eventually into (1) the paraphysis, (2) the dorsal sac, and (3) the pineal eye.

Warren,<sup>23</sup> through studies of *Reptilia*, also supports the view of development from a single bud. He concludes that the pineal eye and the epiphysis of the lizard arise as two outgrowths from the epiphyseal arch, that for the eye being immediately in front of that for the epiphysis. This bud first appears in the second embryonal month.

(Marburg, Schuller, et al ) In reptiles, birds, and mammals, the pineal process consists first of a row of follicles that are empty, and later these become filled with nucleated cells (Munzer) <sup>51</sup>

According to Studnicka, the pineal body is present in all vertebrates with the exception of *Myximoids* and *Torpedo marmorata* D'Erchia,<sup>6</sup> however, finds it lacking in *Torpedo ocellata*, and other authors say that it is not present in *Crocodylia*

#### PAST ANATOMICAL FINDINGS

In man, the body lies just beneath the splenium of the corpus callosum, resting on the superior colliculi of the corpora quadrigemina. It is about 1 cm in length and half as broad as it is long. Its shape may be roughly described as resembling that of a pear or a cone. In other species, its size varies more or less directly with the size of the animal, although relatively larger in the rabbit and guinea-pig than in the cat and dog. Its situation also in animals such as the guinea-pig, rabbit, and in birds is more superficial, owing to the relatively much greater development of the corpora quadrigemina in them, and the relative thinness of the occipital lobes of the cerebrum. The vena magna Galeni accompanies the gland throughout its entire extent, and in the chicken (Foà) and also the guinea-pig and rabbit, the separation of these two structures in an operation for extirpation is impossible.

The pineal is surrounded by a thin capsule of connective tissue, which continues anteriorly as far as the so-called *Schaltstück*, by which the body forms its connection with the taenia habenularum. This capsule was recognized and described by Faivre, and he also described the "globular parenchyma" and "acervulus or sand." Over the *Schaltstück*, which is not a true stalk but an attenuated portion of the anterior end of the body, the covering is ependyma, according to Marburg, whose monograph should be consulted for the finer structure and relation of the taenia to this portion of the pineal.

From the capsule, thin strands of connective tissue penetrate the interior of the gland, forming a meshwork of irregular lobules or follicles in which lie the other elements constituting its structure. The blood vessels accompany these fibrous trabeculae. The lobulation is most evident and most regular in man and the larger animals (calf, sheep), but in the guinea-pig the connective tissue framework is very intricate and not very evident, the gland at first sight appearing to be simply a mass of cells held together by the capsule.

The cellular elements are somewhat varied, and differ slightly in different species, but certain types of cell are common to all. First, there is what may be called the parenchymal cell, or pineal cell proper, a cell whose outline is irregular and hard to make out, owing to its poorly staining cytoplasm. The nucleus is round and stains intensely

with hematoxylin, as does also the nucleolus. The nucleus, in addition, contains many fine granules, on which is based the anatomical belief of the glandular nature of the organ. This glandular nature of the parenchymal cells is brought out by nearly all anatomical observers, being especially marked in birds, according to Sarteschi. Dimitrova,<sup>4</sup> Studnicka, Krabbe<sup>15</sup> and Marburg comment at length on the granules of the nuclei. In a recent contribution, Krabbe also lays stress on the extrusion from the nuclei of pyronuclear granules.

Next to the true parenchymal cells, in point of number, come the glial cells. These form a constant and numerous element in all glands which have been studied by the various investigators, from Kollicker<sup>14</sup> in 1850 to those of the present day. For a more detailed account of the structure of these cells, reference may be had to the works, among others, of Dimitrova, Studnicka, Krabbe,<sup>15</sup> Sarteschi<sup>10</sup> and Marburg. In the calf particularly and in the sheep, there seem to be two zones of glial cells, an anterior, in which the cells are of a larger type, and a posterior in which they are definitely smaller and more numerous.

Among other important structures found in the pineal of certain species (ox, calf, sheep, dog) are the cavities resembling thyroid vesicles (Dimitrova) from which may arise the cysts which have been described by Jordan,<sup>13</sup> Marburg and others.

The so-called sand bodies are another constant and characteristic finding, especially in the pineal of man and the larger animals. Other structures which have been said to occur are sympathetic nerve cells (Cajal,<sup>2</sup> Retzius<sup>16</sup>), cells resembling the latter (Dimitrova), calcifications and lipoid substances (Krabbe), striated muscle fibers (Dimitrova), ganglion cells (Studnicka), and possibly mitochondria (Biondi<sup>1</sup>).

Studies of the paths of secretion of the pineal have been made by Loewy.<sup>20</sup> He injected dye stuffs into its substance, and thus demonstrated three types of spaces: (1) pericellular, (2) interlobular, and (3) spaces connecting the gland substance with extraglandular structures (choroid).

## PHYSIOLOGICAL OBSERVATIONS

### I. ADMINISTRATION OF EXTRACTS

(a) *Acute Effects*.—A limited number of physiological experiments with extracts of the pineal have been reported, and these have, in the main, been negative so far as any striking effect on the bodily activities is concerned.

In 1898 Howell<sup>27</sup> made brief mention of some intravenous injections of pineal extract, in which the effect on the blood pressure was inconstant. Von Cyon<sup>25</sup> in 1903 injected intravenously extracts of the pineals of the ox and sheep. Small doses were said to have no effect

on the blood pressure, but gave a slight tachycardia. In larger doses a slowing of the heart was noted, together with a frequent pulsus bigeminus or pulsus trigeminus, and a fall in blood pressure sometimes occurred. He, moreover, was led to revive the ancient view of a mechanical function which regulates the flow of cerebrospinal fluid from the third ventricle, because of changes observed in its form after electrical stimulation. Krabbe<sup>15</sup> also supports this older theory in a recent discussion of the function of the pineal.

Dixon and Halliburton<sup>26</sup> in 1909 studied the effects of extracts of the pineal bodies of sheep, but fail to say whether the material came from adult or from young animals. The results were relatively negative on blood pressure, heart rate, and respiration, as well as on the volume of the intestine and kidney and on the rate of kidney secretion.

The studies of Jordan and Eyster<sup>28</sup> in 1911 are also negative with regard to any great effect on blood pressure. A relatively slight fall was recorded, together with an intestinal vasodilation, and a transitory diuresis with glucosuria was observed in 80 per cent of the cases.

In 1912 Ott and Scott<sup>31</sup> found the effect of pineal extract on arterial tension, urinary secretion, glucosuria, intestinal and uterine contractions, and pupillary dilatation to be practically negligible. An insignificant vasodilatation of the kidneys was recorded, together with a little increase in the flow of urine.

*Personal Observations of Acute Effects*—With the idea that extracts of very young animals might be more potent than those commonly employed, a series of observations was made with glands from calves and young sheep. The material was obtained fresh from the abattoir, ground up in a mortar and dried in the air. A part was mixed with lactose in the proportions of 1:3, and when used was weighed out as powder and dissolved or taken up in normal salt solution. Medium-sized dogs were used and the injections were made into the left external saphenous vein.

Injections of small amounts (0.1 gm.) gave practically no result. There was a variable, moderate fall in blood pressure, with no effect on respiration or on the flow of cerebrospinal fluid. With larger amounts of the powder (0.5 gm.) a constant fall in blood pressure was recorded, varying from 10 to 24 mm. of mercury. The acute effect of the injection lasted on an average about two minutes, the pressure in all cases showing a subsequent gradual rise to normal over a period varying from ten to fifteen minutes. In no case was there a subsequent pressor response.

In order to test the effect on the flow of cerebrospinal fluid, the Cushing-Weed method of puncturing the third ventricle was employed, each drop being recorded as it fell from the cannula by a marker on the drum. The effect on the cerebrospinal fluid was that which might



be expected merely from the concomitant fall in blood pressure, namely, a slowing of the flow, or in some cases an absolute stoppage. The injections made with extracts of the fresh glands before drying, either by boiling or extracting in warm salt solution, were in all essentials similar to those of the dried powder. In order to see whether the effects recorded were due to the pineal extract itself or to the cholin content of the gland,  $\frac{1}{100}$  grain atropin was used in a series of injections along with the pineal extract. The results obtained from these injections varied considerably, but in all cases a slight fall was demonstrable, and in at least one case the fall was measurably as great as that caused by an injection of the extract without the atropin fifteen minutes previous.

It was found, therefore, in agreement with our predecessors, that intravenous injections of the extracts of the pineal body of young animals cause a constant but relatively slight fall in blood pressure. The injection causes no increase in the flow of cerebrospinal fluid and the fall of blood pressure, moreover, is not due entirely to the cholin content of the gland.

(b) *Prolonged Effects*—Several investigators have administered pineal substance to animals over long periods, either by the method of feeding the dried gland by mouth or injecting extracts of it intraperitoneally.

Dana and Berkeley<sup>12</sup> in conjunction with Goddard and Cornell carried on a series of such experiments and conclude that the ingestion of powder made from the pineal body hastens the growth of young animals. The animals used were young guinea-pigs, kittens and young rabbits. In all cases the subjects, which were fed the pineal powder, gained a relatively greater amount in body weight than the controls over the various courses of observation, extending from two and one half to five months. The actual figures show that the gain of fed animals over controls varied from 7.5 to 20 per cent.

As a result of these investigations, pineal gland substance was administered to a series of fifty defective children and they felt that it proved of value, though no results were obtained in cases of frank idiocy or gross physical defects. Improvement was noted in cases of simple retarded mental development and mongolism. The controls gained more in body weight, and the subjects more in mental capacity. They could not be certain of any mental defect in children which might be ascribed to hypopinealism or apinealism.

In 1914 McCord<sup>46</sup> studied the results obtained by feeding powdered extract to young guinea-pigs, young chickens and puppies. The extract was made from the pineal glands of "young adult cattle," dried and mixed with lactose. A noticeable overgrowth occurred in body weight of the animals fed with the extract over the controls. His statistics

show a 23 per cent gain for the guinea-pigs fed with pineal over their controls, and in chickens also he says there was a noticeable increase in size in those fed on the gland substance. He notes further that among the females which received the pineal powder there is a greater tendency to earlier pregnancy than among the controls. His investigation with puppies was unsatisfactory, owing to distemper. In more recent papers<sup>47</sup> he confirms his earlier results. In his later series hypodermic injections of pineal extract were substituted for the oral administration of the gland, and the guinea-pigs so injected showed 26 per cent gain in weight over controls during the six weeks of observation.

J. B. Boehm, working in this laboratory during the past year, has also studied the effect of prolonged oral administration of pineal gland substance to guinea-pigs and rats. His results were conflicting, in that in some cases the fed animals showed greater development of their genital organs than the controls, while in other cases the controls outstripped the animals to which the pineal was administered.

## II EXPERIMENTAL EXTIRPATIONS

(a) *Previous Observations*—The literature appears to contain but seven references to any attempts at experimental removal of the pineal body. Sarteschi<sup>38</sup> in 1910 reported negative results on a series of eleven rabbits, only two of which lived, and in only one of these was the gland thought to be totally extirpated. In 1913, however, he succeeded in removing the pineal from two puppies and three guinea-pigs<sup>39</sup>. One puppy was said to have gained definitely in weight over its control, and its sexual development accelerated. At necropsy its testes were much larger than those of the control. The other puppy had no control, but its testes were said to be much larger than normal, when it was sacrificed before reaching adult size. As to the guinea-pigs, the author found an increase in weight of body and in the size of the testes in one experimental animal over its control. The testes of the other two guinea-pigs were said to be "well developed" when sacrificed, but there appear to have been no controls. There were no changes in the other glands of internal secretion.

Biedl<sup>48</sup> in 1910 attempted without success to extirpate the pineal in puppies. No changes were noted in the three survivors of his series. The following year Exner and Boese<sup>35</sup> reported negative results in a series of ninety-five young rabbits, of which only six survived to maturity and these showed nothing which could be demonstrated as a departure from normal.

Foà<sup>36</sup> in 1912 reported the only notable changes which up to that time had been recorded after total experimental pinealectomy. He succeeded, with chickens, in having three cocks and twelve hens live to maturity after extirpating the gland. No changes occurred in the hens

The pinealectomized cocks showed various evidences of hastened maturity. They crowed and gave evidence of sexual instinct from forty-two to seventy-nine days before their controls. There was a marked relative hypertrophy of the combs and testes of the experimental over the control cockerels.

Two years later Foà added some confirmatory results to his earlier work.<sup>17</sup> In a second series two males and five female chickens survived pinealectomy. Again no changes were observed in the case of the females, but the two pinealectomized males showed a much greater increase in the size of their combs and testes than did their controls. The author also attempted to remove the gland in eight young rats, and of the four survivors, three were males. These animals apparently gained in body weight over controls up to a certain length of time after operation, when the weights of both became about equal. One rat showed an increase in the weight of its testes over the control. Microscopically, the testes of pinealectomized animals, both chickens and rats, showed relatively larger canaliculi and tubules than did their controls. No apparent changes occurred in the other glands of internal secretion.

A series of observations on canine pinealectomy were made by Dandy under Dr. Cushing's suggestion in the Hunterian Laboratory in Baltimore in 1912. Some successful extirpations were achieved, but the results were negative. The method has subsequently been perfected by Dandy, who records a series of further experiments with equally negative results.<sup>10</sup> Thus, though Sarteschi's and Foà's experiments with rats are suggestive, no conclusive changes have been observed as yet in mammals.

(b) *Personal Observations*—The topography of the pineal region in young dogs and cats was studied with a view to the most favorable surgical approach, but after numerous operative trials which resulted in incomplete resections, further work on these animals was abandoned. The same experience was had with young rabbits, and although the operative results were slightly better than in the case of the puppies, they were on the whole equally unsatisfactory. The operation was done in one stage, and in a majority of cases the gland was completely extirpated, but no animal survived the inevitable hemorrhage more than forty-eight hours. Even the controls, which were subjected to a simple decompression over the pineal region, usually succumbed within a week.

#### GUINEA-PIG SERIES

The operative results with these animals, however, were very much more successful, and the complete removal of the gland was accomplished in a large percentage of cases. The animals when operated on varied in age from 2 days to 6 or 7 weeks, and usually the experimental and control animals were members of the same

litter. If at least two males or two females could not be obtained from the same litter, the animals which were chosen for operation were picked from the same breed, and at the start were as nearly as possible equal to each other in weight and age. The difference in weight in such animals was never more than a few grams, and in age never more than two to four days. The two sets of experimental and control animals were kept and fed under identical conditions, the cages of both being of the same size and in the same situation, and the amount of food for each lot was weighed out equally.

On the whole, the animals did very well, considering that they were operated on at so early an age, and if lived over the first forty-eight hours they usually lived until sacrificed, although a few of both experimentals and controls died after the course of several weeks, due to intercurrent causes. In all, 144 pigs were operated on, and of these an attempt was made in 82 to extirpate the gland, while in the remaining 62 a control trepanation was performed. The larger number of experimental animals is due to the fact that the operation on them being more severe, there were more immediate casualties, necessitating a greater number of subjects for operation. Of the 82 experimental animals, 48 lived to maturity or until sacrificed, while of the 62 controls, 42 lived an equal length of time as their experimentals.

In nearly every instance postoperative death was due to hemorrhage from the large vein of Galen. The mortality is necessarily high. Exner and Boese in 1911 quote 75 per cent of immediate deaths in young rabbits, Sarteschi in his first report shows 72 per cent deaths with the same species, while in his more recent work his mortality was 87.5 per cent with guinea-pigs and 80 per cent with puppies. Foà's percentage of deaths from operation on chicks was 76, but in 1914 he reduced this to 30 per cent, while of the eight young rats mentioned in his last paper, four died, a 50 per cent rate.

#### TECHNIC

As perfect asepsis as possible was employed, and no infections developed in the entire series. Ether was the anesthetic used throughout. The skin was prepared by shaving and by applying 70 per cent alcohol, and a piece of sterile gauze dampened in 1:1,000 mercuric chlorid was placed over the whole animal. A small opening in the gauze was then made over the operative field.

After a median line incision over the posterior end of the skull, the periosteum was scraped back with a blunt knife and a chip taken out of the underlying bone down to the dura with a sharp knife. The area was further enlarged until the superior longitudinal sinus was exposed from about its midpoint to where it joins the two lateral sinuses between the posterior end of the cerebrum and the anterior end of the cerebellum. The greater part of the occipital bone was removed in one piece, so that the pineal region was exposed fully. The superior longitudinal sinus was now ligated in two places anterior to the two lateral sinuses and divided with the dura between the ligatures. The posterior flap of dura thus formed was then retracted, exposing the gland. This was grasped firmly with a "mosquito" clamp and gently pulled

out, sufficient tension being exerted to disengage it from its adherent structures without causing it to break apart itself. The gland was put into 10 per cent solution of formaldehyd and subsequently sectioned. A good deal of hemorrhage always followed the extraction of the gland, but was usually controlled by the pressure of cotton pledgets taken from hot salt solution. The dural flap was then replaced and the skin sutured. For the controls, a similar operation was performed with ligature of the sinus, but the dura was not opened.

TABLE SHOWING AVERAGE WEIGHTS OF EXPERIMENTAL AND CONTROL ANIMALS AT TIME OF OPERATION AND WHEN SACRIFICED

Pair No	At Operation			When Sacrificed						
	Age in Days	Body Weight		Age in Days	Body Weight		Testes		Seminal Vesicles	
		Op'd, Gm	Control, Gm		Op'd, Gm	Control, Gm	Op'd, Mg	Control, Mg	Op'd, Mg	Control, Mg
1	49	240	237	85	383	355	1,830	1,700	2,210	1,030
2	35	179	216	84	284	296	610	560	430	320
3	35	235	279	84	350	351	1,185	910	1,170	570
4	38	207	105	91	325	340	1,930	730	2,280	1,080
5	14	142	153	63	315	309	1,050	830	910	1,050
6	18	132	117	63	265	240	680	470	630	220
7	14	156	161	56	288	315	850	730	940	420
8	7	120	103	56	222	174	560	400	370	260
9	10	170	158	52	237	211	380	270	220	220
10	7	91	80	19	118	131	160	170	130	130
11	10	129	140	15	148	161	140	170	120	150
12	5	115	85	77	254	215	930	710	390	350
13	{ 7* 10 }	98	113	77	240	213	920	720	400	340
14	{ 10* 7 }	145	129	63	209	225	490	480	280	350
15	{ 10* 7 }	110	109	70	245	261	1,100	1,100	970	500
Total		2,269	2,308		3,878	3,800	12,815	9,950	11,450	7,000
Average		151.2	153.8		258.5	253.3	851.3	663.3	763.3	466.6

\* Pinealectomized animal

After operation, the experimental and control animals were put into separate cages, males and females in each lot being kept together from the start, so that an idea of any differences in time of breeding could be noticed. Each animal was weighed weekly. The age at which the various pairs of experimental and control pigs were sacrificed varied from seven and one half to fourteen weeks in the case of males, but females were often allowed to live a much longer period so as to note

the date of their first parturition. When sacrificed, the animals were chloroformed and the testes and seminal vesicles carefully removed and weighed. These, together with the other endocrine glands, were immediately put into Zenker's solution, and after embedding in paraffin, sections were cut from exactly corresponding parts of each organ. The brain of the experimental animals was also removed, together with the meninges, at the time of necropsy, and serial sections cut through the whole of the pineal region so that any trace of remaining pineal gland could be discovered. In fifteen males and twenty females of the series the gland was thus found to have been totally extirpated. It is, therefore, to these animals, with their controls, that the record of our results is confined.

**Results (males)** Taken as a whole, very little difference was noted in the body weights of the experimental and control animals. As will be seen by the accompanying table, the average weight of

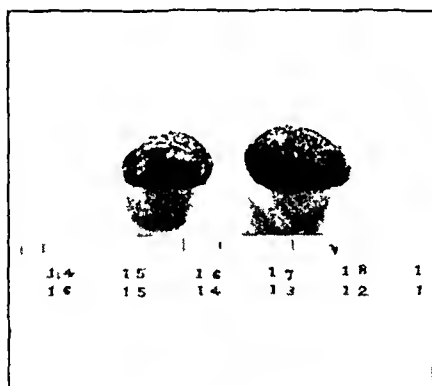


Fig 1—Showing testes of guinea-pigs (Pair 1) aged 14 weeks, seven weeks after operation. Right pinealectomized animal (Slightly reduced)

experimentals at the time of operation was slightly less than that of the controls, and when sacrificed from the fourth to the seventh week after operation there was a slight gain in favor of the pinealectomized animals, but both figures are possibly within the normal limits of variation. Both Foà and Sarteschi, however, record a gain in weight of pinealectomized over control animals, so our findings, though not striking, accord with theirs.

In regard to the growth of the genital organs, a much more noticeable increase took place in favor of the pinealectomized animals. As shown by the table, the total weight of the testes of the experimental animals was 12,815 mg against 9,950 mg total for the controls. This makes an average of 854.3 mg for each experimental pig against a 663.3 mg average for each control. This difference will be seen in the photographs of several of the various pairs of testes of experimental and control animals (Figs 1, 2, 3 and 4).

It will be noted in the table also that the experimental pigs showed a marked increase in the size of the seminal vesicles over those of the controls No mention appears to have been made by other investigators

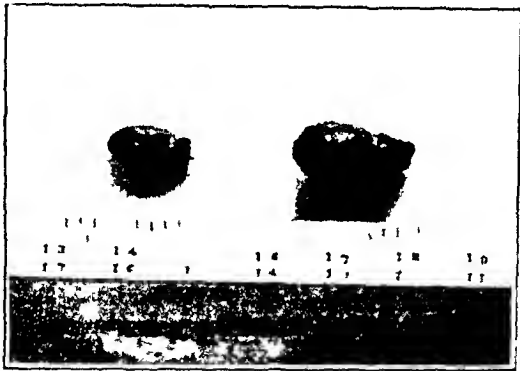


Fig 2—Showing testes of guinea-pigs (Pair 4) aged 13 weeks, seven and a half weeks after operation Right pinealectomized animal (Slightly reduced)

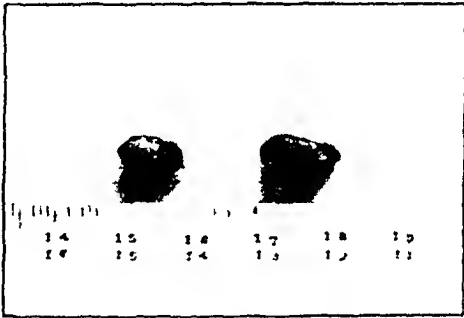


Fig 3—Showing testes of guinea-pigs (Pair 6) aged 9 weeks, fifty days after operation Right pinealectomized animal (Slightly reduced)

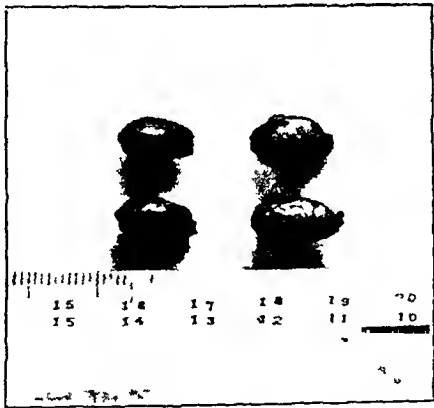


Fig 4—Showing testes of guinea-pigs (Pair 12) aged 11 weeks, seventy-two days after operation Right pinealectomized animal (Slightly reduced)

concerning these organs, which in the case of the pituitary studies made by Goetsch<sup>43</sup> in this laboratory were found so greatly enlarged Our pinealectomized animals showed a total weight of the seminal vesicles

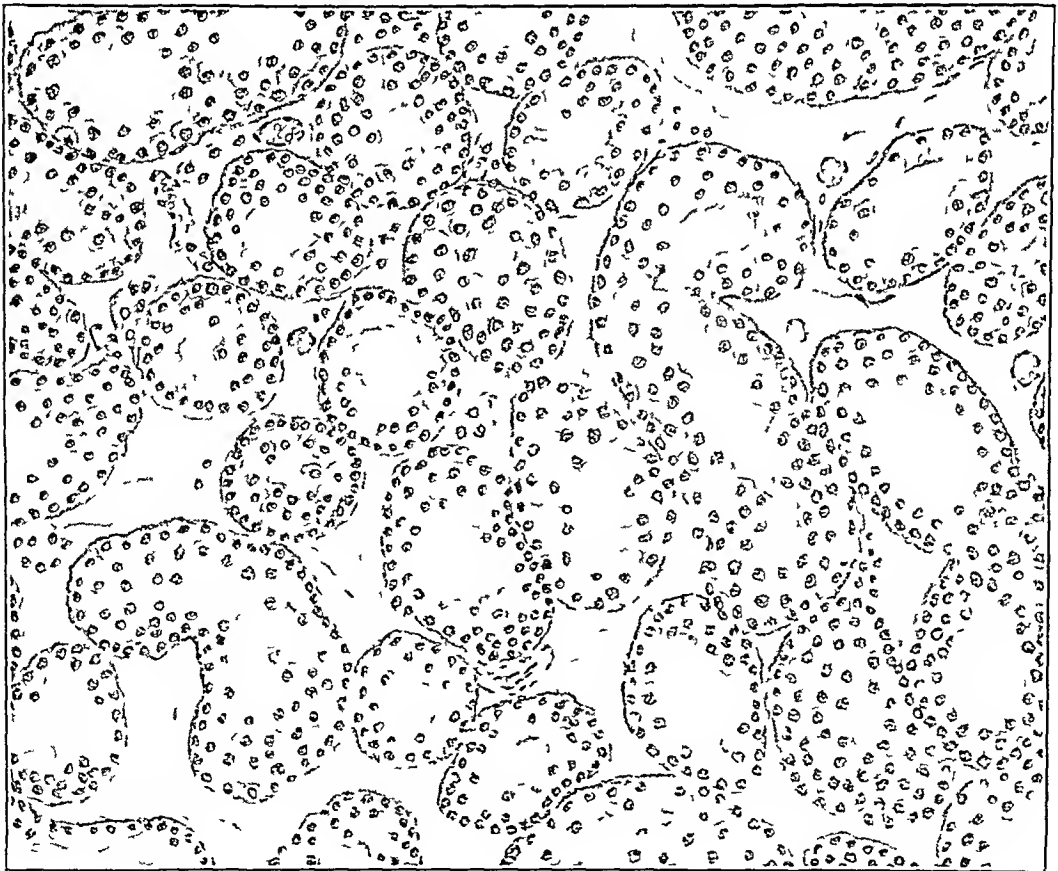
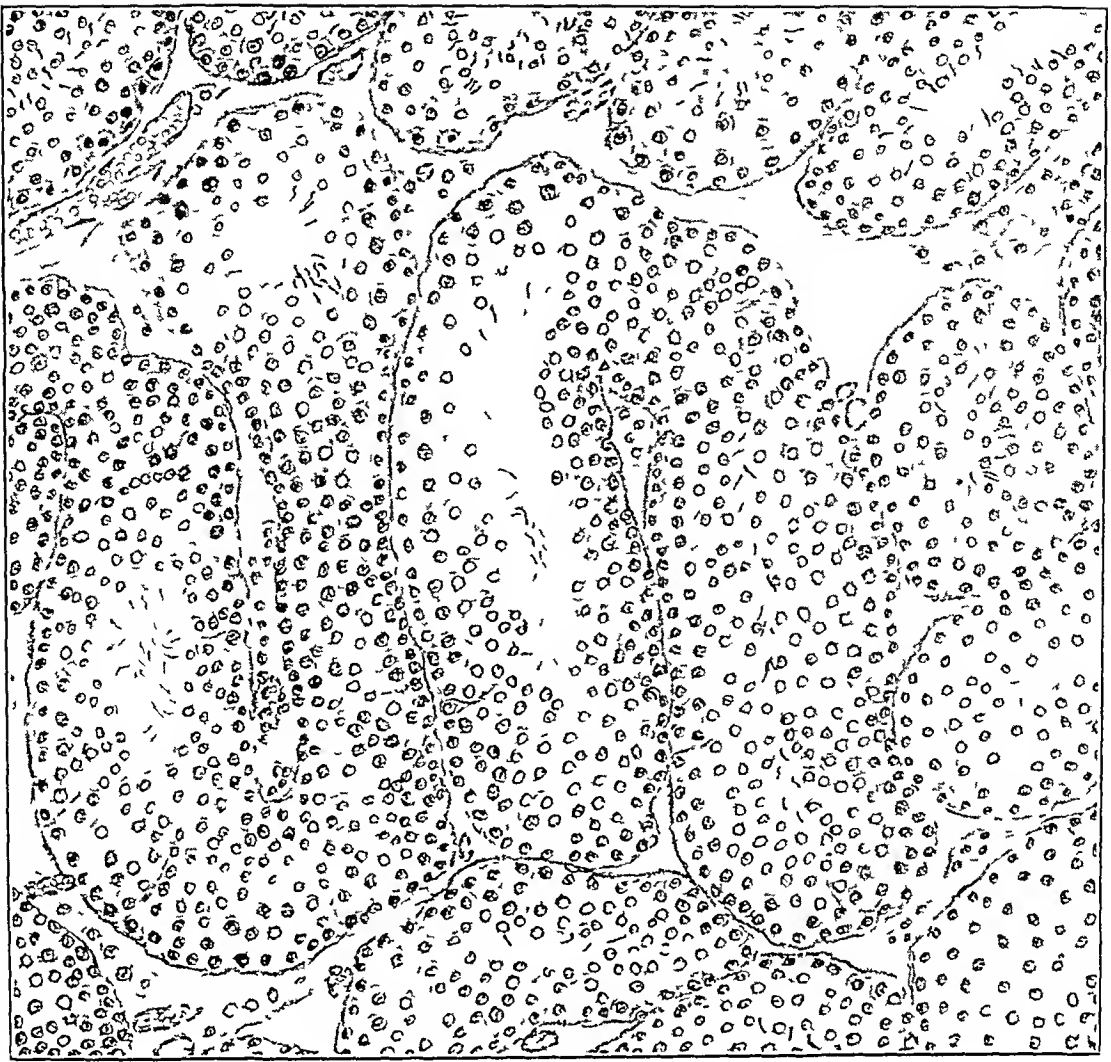


Fig 5—Sections through corresponding portions of testes of guinea-pigs (Pair 4) aged 13 weeks. Note large size of tubules with many layers of spermatogenic cells and tails of spermatozoa in pinealectomized animal (upper drawing) ( $\times 100$ )



of 11,450 mg against the controls' 7,000 mg, or an average of 763.3 mg for the former against 466.6 mg for the latter. Again, the photograph serves to emphasize the difference which the scales record.

Microscopically, the differences in the testes of the experimental and control animals were perhaps not so marked as might be expected from a comparison of their gross size and weight. Nevertheless, in this respect also, there were changes which indicate a hastened development of the organs under consideration (Fig. 5). The most marked differences occurred in pigs which were sacrificed between the ages of

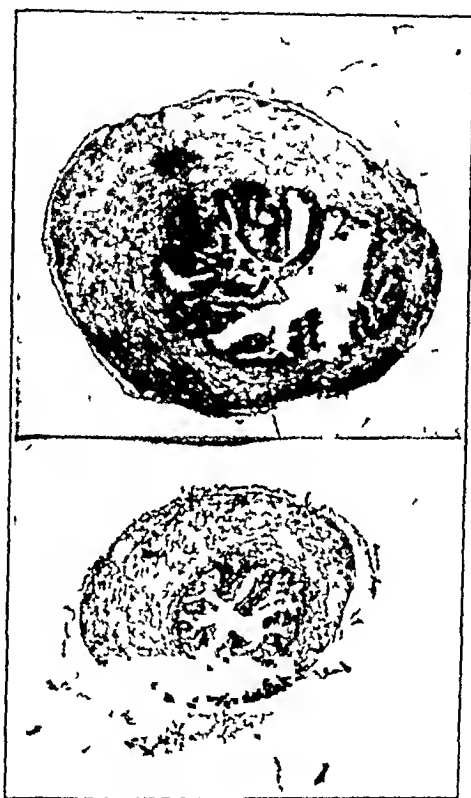


Fig. 6—Sections through corresponding portions of seminal vesicles of guinea-pigs (Pair 8) aged 8 weeks. Note larger size and more advanced state of epithelial lining of lumen in pinealectomized animal (upper photo) ( $\times 25$ )

9 and 11 weeks. If sacrificed before this age, practically no microscopical differences could be detected, while later than eleven weeks the difference again became very slight owing to the proximity of normal maturity.

When taken during the age of maximum difference, the testes of pinealectomized animals show relatively large tubules, their lumina almost entirely filled with the many layers of spermatogenic cells in all stages of growth. Active spermatogenesis is evident. Interstitial cells are abundant, but cannot be distinguished in size or in amount from those of the controls. The tubules of the controls are definitely smaller,

when exactly similar portions of the testes of each are studied, and the layers of spermatogenic cells in the lumina are fewer by far than is the case with the experimental animals. Occasionally there are a few mature spermatozoa but these are rare and there is much less uniformity of development portions of the testis showing tubules in a very immature stage without even a beginning spermatogenesis.

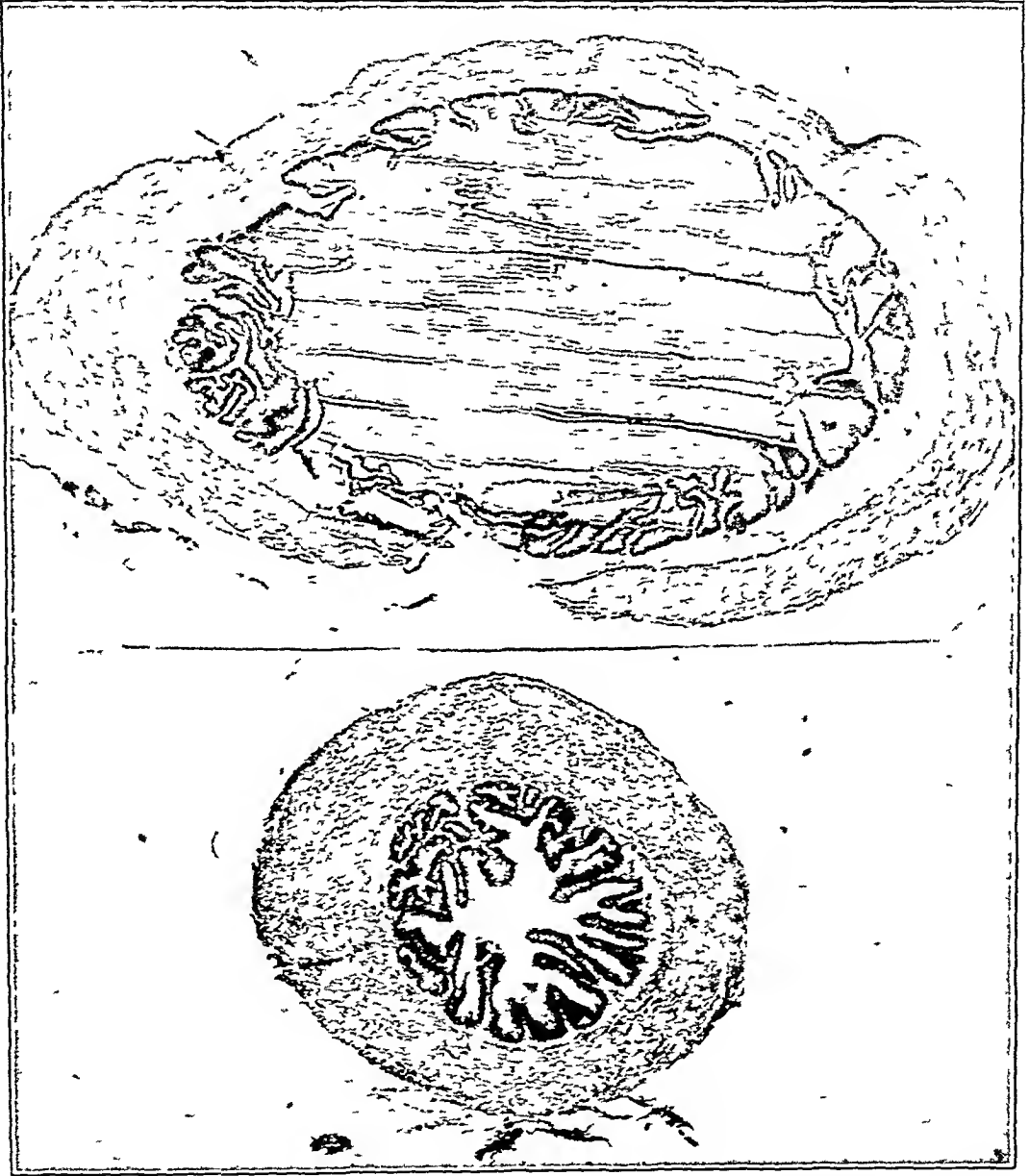


Fig 7—Sections through corresponding portions of seminal vesicles of guinea-pigs (Pair 6) aged 9 weeks. Note larger size and thinning of walls due to collection of secretion in lumen in pinealectomized animal (upper photo). Control shows small size and thick walls of immature vesicle and no evidence of secretion from epithelial lining. ( $\times 25$ )

The microscopic picture in the seminal vesicles of the two sets of animals was far more striking than that of the testes. Here no particular age of maximum difference could be identified, except that earlier

than 8 weeks of age, the vesicle always appeared immature in the case of both. Beyond this age there was a rapid change in the experimental animals, manifested by an enlargement of the lumen of the vesicles at the expense of the thickness of their walls. The cells of the lining mucous membrane were seen to increase in height, while in most cases there was an abundant secretion of colloid material completely filling the lumen. The difference between this picture and that of controls is clearly shown in Figures 6 and 7. Here the cross section of the vesicle, always taken at a corresponding point to that of the experimental, is noticeably less, the walls are thicker and the lumen smaller, as in the immature type. That the lining cells have not yet begun to secrete is evident from the total lack of colloid secretion in the lumen.

**Results (females)** In accordance with the observations of other investigators, no differences could be made out in size or weight of the female genital organs, nor was there a demonstrable difference when these tissues were studied under the microscope. In regard to body weight, it may be said of them that a similar curve was shown as in the case of males, excluding the ones which became pregnant, as here, naturally, a normal rapid increase was evident.

As to physiological evidence of hastened maturity in females, the incidence and termination of pregnancy is the only factor which we can quote, and here our figures are inconclusive, owing to the fact that in most cases the males were sacrificed before the age of full sexual maturity was reached.

Of the twenty females in which total pinealectomy was shown to have been accomplished, three became pregnant, while out of the same number of controls there were but two. All three experimental pigs were delivered of their young ten days or more before either of their controls gave birth, the earliest of the experimentals being delivered three weeks before either control. When it is considered that the normal period for guinea-pigs to reach sexual maturity is about nine weeks, it will be seen that, in the above instances at least, this period was shortened one sixth to one third.

From the experiences with young guinea-pigs several difficulties were obvious. First, the litters being very small—usually not more than two—it was hard to get a large series with absolute controls. Second, as the time between the birth of guinea-pigs and their arrival at normal maturity is quite short, there was little time to observe the changes which might develop due to the influence of the pineal. Lastly, the relatively long, thin pineal gland of guinea-pigs made complete extirpation very difficult because of its tendency to break when traction was exerted on it.

## RAT SERIES

For the above reasons, a series of operations on young rats was undertaken, and although an epidemic ruined nearly all of the experiments, it was immediately evident that, excluding such an unforeseen factor, these animals on the whole made the more ideal subjects for pineal experimentation. Litters are large and the interval between birth and sexual maturity is far longer than in guinea-pigs. The pineal gland itself is much shorter and less fragile, and can be picked out easily and surely with a pair of small forceps.

As previously mentioned, an epidemic broke out among the cages of rats, and in order to get a fresh start after thorough disinfection, the few survivors were sacrificed earlier than had been intended. Among these, only one or two showed any changes which might be attributed to disturbance in pineal secretion.



Fig 8—Showing testes of rats (Litter 13) aged 9 weeks, four weeks after operation. Right pinealectomized animal ( $\times 2$ )

Two males of Litter 13 were sacrificed at the age of 9 weeks. Complete pinealectomy had been performed on one, and a control operation on the other a month previously. Their sizes and weights at the time of operation were almost identical. When sacrificed, the pinealectomized animal weighed 37 gm, as against 28 gm for the control. The testes of the former were also much larger than those of the latter, weighing 410 mg to 250 mg for the control (Fig 8).

Two males of Litter 12, a pinealectomized and a control, showed no differences at the age of 9 weeks, these animals also having been operated on a month before. The testes of each weighed 300 mg.

Three males of Litter 22 also showed very slight differences. They were sacrificed when 7 weeks old, their operations having been performed only two weeks previously. Of the three, the pinealectomized

weighed 36 gm when sacrificed, as against 35 gm and 31 gm, respectively, for the two controls. The testes of the experimental rat weighed 280 mg, while those of the controls weighed 260 mg and 280 mg, respectively.

In Litter 23 there was but one survivor, a pinealectomized male, and this animal, although sacrificed when 6 weeks old and only two weeks after operation, showed an increase in body weight from 23 gm to 31 gm, and its testes weighed 410 mg. Another single, male, pinealectomized survivor occurred in Litter 17. This animal was sacrificed at the age of 9½ weeks, or three and one half weeks after operation. Its body weight was 29 gm and that of its testes 280 mg. Interesting comparisons with these last two cases, although not actual controls, are the two surviving members of Litter 11. Both these animals had a control operation performed at the age of 5 weeks, and were sacrificed when 9 weeks old. Their weights were 25 and 40 gm, respectively, while the testes of the one weighed 280 mg and of the other 300 mg.

Aside from the demonstration of the comparative ease of the operation, which will make this species the most desirable for future studies, the results for our immediate purposes are inconclusive. Can the changes which have been observed in these experiments be attributed to the loss of the pineal gland, or may they be attributed to some other injury of glandular or nervous tissue? The only other intracranial organ which is known to influence bodily growth and sexual development is the pituitary body, and it is conceivable that, as a result of the operation which has been described, some secondary changes might occur in that structure, due, possibly, to a postoperative hydrocephalus scar formation, but such a condition has never been observed and, furthermore, it would have led to changes the reverse of those we have seen, namely, to skeletal undergrowth and delayed sexual development. In our series of guinea-pigs the pituitary was studied microscopically and no departure from the normal was noted.

### CONCLUSIONS

- 1 Total experimental pinealectomy is possible in guinea-pigs and rats.

- 2 Pinealectomized male guinea-pigs show a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of the testes and seminal vesicles, over control pigs of the same litter.

- 3 Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, show a more advanced physiological state than their controls.

4 The pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight

5 For several reasons, young rats are likely to prove better subjects for experimental pinealectomy than young guinea-pigs, and some evidence of hastened maturity has been obtained in this species

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# STUDIES ON THE PINEAL GLAND

## II CLINICAL OBSERVATIONS <sup>1</sup>

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### INTRODUCTORY

The clinical aspects of pineal tumors have been abundantly discussed since 1909, when Frankl-Hochwart<sup>19</sup> suggested the possibility of a pathognomonic syndrome. Marburg<sup>40</sup> especially has developed the subject, emphasizing the association of adiposity, which he regards as an indication of overfunctioning of the gland. To this we shall return in the discussion of one of the cases here reported.

The salient factors of pineal symptomatology may be gleaned from the reports of about seventy cases of tumor of the gland. Of this number only twenty-two occurred before the age of puberty and these, therefore, represent the source of evidence of that special train of symptoms which we have come to associate with pineal disorders, namely, premature development in the realm of both primary and secondary sexual characters. In several of these cases, moreover, principally in the earlier reported ones, the case records are insufficient or wanting, and in five others no reference is made to the sex organs, although certain metabolic symptoms are noted. Of these, adiposity, drowsiness and polyuria are the most frequent, suggesting at once an implication of the pituitary, but the imperfect records preclude any possibility of settling this question at present. Regarding the other cases, of which there are about ten, we find that all but one are in young boys between the ages of 2 and 12 years. The exception is Marburg's case, a girl 9 years old.

Following Marburg's classification in his later paper (1913),<sup>41</sup> the symptoms recorded may be put down under three headings:

- 1 *General*—These include all the usual signs of intracranial pressure, usually due to a secondary hydrocephalus, and need not be given in detail.
- 2 *Neighborhood*—Of these the more important are dependent on pressure on the corpora quadrigemina, giving various oculomotor paralyses and pupillary disturbances, and also those by which the cerebellum is secondarily involved, with ataxia as the main symptom.
- 3 *Constitutional*—It is here that we find the various changes for which the name "macrogenitosomia praecox" has been suggested. Coupled

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with a general bodily overgrowth, the size of the primary sex organs is the most striking feature in the records of these cases. The penis and the testes are frequently described in these children as of adult proportions, and both pubic and axillary hair is noted to be similar in extent and abundance to that of maturity. Again, the change in voice to that of deep masculine type is recorded in one case as early as 5½ years. Mental precocity is also a well-marked symptom.

To sum up, then, the above syndrome usually occurs in boys before the age of puberty, and at necropsy in all cases a tumor replacing the pineal gland has been found. In the case of the girl, no disturbance of the sexual organs was apparent, adiposity being the only metabolic finding. If we are right in assuming that the pineal is a gland, and that its secretion exerts any influence on bodily processes, such evidence as we have would seem to indicate that this influence is exerted on inhibiting physical and mental adolescence.

#### REPORT OF CASES

During the past two years the following three cases have been observed in the surgical service at the Peter Bent Brigham Hospital. In one of them a tumor of the pineal was shown to be present at necropsy. The other two patients are still living, but with symptoms and signs sufficiently suggestive of pineal disturbance to justify their inclusion here.

It is quite possible that these conditions may be more frequent than is commonly supposed. Two cases have already been recorded by Dr. Cushing<sup>11</sup> in which the surmise of a pineal tumor was made. These gave the usual clinical picture. The two suspects among our present three cases are as follows. The first of these is a young girl.

*CASE 1—Surg. No. 1341. Precocious adolescence, overgrowth, cranial enlargement, Callosal puncture.*

June 1, 1914, admission of Virginia G., aged 11, referred by Dr. H. T. Pershing of Denver, Colo.

*Family History*—The patient's father and mother are living and in good health. There are two other normal children in the family, a boy and a girl, both younger than our patient.

*Personal History*—A full term baby, born without instruments and without particular difficulty, bottle fed, walked and talked at 18 months. At the age of 1 year it was noticed that her head was unusually large, and a diagnosis of hydrocephalus made by the family physician. Her body then began to develop abnormally, so that she has always been large for her age. Her mother describes her appetite as enormous.

Two years prior to admission she had what was apparently a period of polyuria. Subsequently she had a bad attack of typhoid fever, with relapse, lasting six months. Eyesight has been poor since babyhood and she has worn glasses for some time. Apparently there was an external strabismus of the left eye which was corrected by operation two years previously.

There has been a persistent but not increasing weakness of the right hand and arm since birth, so that the child early learned to use the left hand almost

exclusively, even in writing For many years, also, she has been troubled with headaches, which have been frontal and bitemporal in situation There has been no concomitant nausea, or vomiting, but some slight dizziness These headaches have been less troublesome during the past two years

Along with the overgrowth of the body there has been a precocious development of the secondary characters of sex In August, 1913, when hardly 11 years old, the child first menstruated and she has since continued to do so regularly Her bust became rounded and her bodily configuration was that of a girl beyond the ordinary age of puberty The growth of pubic hair also started Mentally, however, she was still a child, although not backward in school work She finds mental application rather difficult Her weight a year prior to admission was 98 pounds



Figs 1 and 2—Case 1 Patient, aged 11, height, 152 cm , weight, 52.3 kg

*Physical Examination*—A very well nourished and decidedly overgrown girl (Figs 1 and 2) Height, 152 cm (average normal for female of 11.5 years, 138.9 cm (Boas) Weight, 52.3 kg (average normal, 33.8 kg), skin soft, moist, and pigmented, general increase in the subcutaneous adipose layer, the body looking plump and abdomen full, head very large, especially full in the frontal region, and definitely asymmetrical, the whole temporal bone of the left side being much more prominent than its fellow, neck full in the region of the thyroid and the isthmus of the gland palpable

The breasts were very large and firm, areolae pink, the whole corresponding to the growth obtained at 15 or 16 years of age, pubic hair fairly abundant, and axillary hair present to a slight degree, but hair over the body in general lacking, hair on the scalp fine, silky, and abundant The general contour of the body was that of a girl well past the age of puberty Examination of

the fundi showed unusually large disks. On the left there was evidence of an old choroiditis with marked pigment upheaval and irregular shaped disk. Both disks were markedly pale, suggesting a primary atrophy.

In other respects the general physical and neurological examinations were negative.

The Roentgen-ray examination showed a hydrocephalic skull with signs of pressure. The sutures were plainly visible. The sella turcica showed very definite enlargement, the anteroposterior diameter being about 20 mm. The floor of the sella was more vertical than normal. The dorsum sellae was short but distinct. The clinoid processes could be made out. The metacarpal bones and phalanges were long and slender. There was a shadow in the region of the pineal body, presumably calcium deposit.

Urine negative, blood pressure and hemoglobin normal, differential blood count showed 6 per cent eosinophils.

June 10 a callosal puncture was performed without altering her condition. She was discharged June 19, 1914.

*Comment*—In this case, we have no positive means of knowing whether or not the pineal is the organ mainly at fault. The history and findings, however, are suggestive, and conform to the symptom complex of Frankl-Hochwart, except that the patient was a girl. Adiposity, though not great, was present to a definite degree, this, with the other points, making the case very similar to Maiburg's.

An increase in the eosinophilic leukocytes should be mentioned, as attention will be called to this point in connection with Case 3.

The following case was also regarded as possibly one of macrogenitosomia praecox.

*CASE 2—Surg No 119 Unusual precocity of adolescence and overgrowth Epilepsy Exploratory operation*

May 17, 1913 Admission of Max W, aged 7½, referred by Dr T H George of Cleveland, Ohio, with the complaint of precocious adolescence and epilepsy.

*Family History*—Father and mother were living and well. The father was of small stature. There were two other normal boys in the family.

*Personal History*—Birth normal and noninstrumental, weight at birth said to be 13 pounds. It was remarked a few days later that his genitalia were noticeably large. When 9 months old he had a bad fall down a flight of steps, but apparently suffered no immediate ill effects. There was no serious illness other than the present trouble.

Growth was rapid, and the patient had always been the tallest of his class in school. Three teeth appeared at 3 months of age and the second set was complete at the age of 7. When 3½ years old the voice had assumed adult characteristics.

Pubic and axillary hair were first noticed at two years of age and increased steadily in amount. Evidences of sexual instinct occurred at the age of three and a half. Masturbation was a continued feature. The disposition had always been irritable and stubborn.

*Present Illness*—First evidence of epileptiform seizures occurred at the age of 3 years. These attacks consisted in an initial, momentary grimace, with groaning, turning of head to right and temporary loss of consciousness. Occasionally headache accompanied the seizures. The duration of attacks was thirty seconds to three minutes. They increased in frequency from the time of their onset until the present.

*Physical Examination*—Although only  $7\frac{1}{2}$  years old, the patient looked like a boy of 15 or 16 (Fig 3), weight, 352 kg (average normal for age, 23 kg), height, 145 cm (average normal for age, 119 cm), circumference of head, 53 cm, axillary hair present, abundant "down" on upper lip, pubic hair thick and of mature, masculine type, but did not extend up on abdomen, external genitalia markedly overdeveloped, in no way differing from those of an adult male, flaccid penis, 9 cm in length, thyroid cartilage prominent and thyroid gland distinctly palpable, teeth in good condition, second set fully established

The fundi were slightly hyperemic, marked nystagmus to the right, voice deep and masculine, blood and urine examinations normal

*Subsequent Notes*—From three to six epileptiform attacks were noted daily, patient's disposition troublesome and mischievous Discharged, untreated, May 30, 1913



Fig 3—Case 2 Patient, aged  $7\frac{1}{2}$ , with father, height, 145 cm, weight, 352 kg

June 17, 1914 Readmission, symptoms increased, headache more frequent, seizures occurred oftener, weight, 394 kg, height, 145 cm

Roentgen-ray examination of hands and feet showed development corresponding to that at the age of 18 years, inner aspect of skull somewhat irregular, venous channels plainly visible, sella was 6 mm deep with antero-posterior diameter of 10 mm, clinoid processes distinct

June 27, 1914 Operation puncture of right lateral ventricle, arachnoid very wet, membrane grayish and thickened, 20 cc fluid secured from puncture, fluid not under tension A small section of tissue was removed from testis for histological examination

July 13, 1914 Second operation exploration of right hemisphere, dura appeared normal, brain under normal tension, arachnoid grayish and thickened, especially anteriorly where it was excessively vascular By pricking the membrane a large amount of fluid was milked out The process was evidently an old meningo-encephalitis with convolitional atrophy

*Subsequent Notes*—Convalescence uneventful Convulsions continued, but not so frequent, no headache since operation Examination of section of testis showed active, adult type with hyperplasia of interstitial cells Discharged July 31, 1914

*Comment*—In this instance we are as yet unable to say what part the pineal may or may not be playing in the syndrome Clinically, however, we are dealing with a symptom complex similar to that characterizing a pineal lesion, but without adiposity The sexual side of the picture is decidedly in the foreground There has been little intellectual attainment, the latter sphere having been greatly limited by the boy's environment

In our third case the lesion was certified in full

CASE 3—Surg No 709 *Precocious adolescence Intracranial symptoms with diagnosis of tuberculous meningitis Xanthochromia Necropsy Pineal tumor*

Dec 22, 1913 Admission of S K B, aged 12, referred by Dr J B Pratt of Boston, with the complaint of nausea and vomiting, intermittent headaches, and blurring of vision of two months' duration

*Family History*—A younger brother of the patient had died two years before, aged 5, from an "acute infection starting with a nasal discharge" The patient's father is a physician and he described this illness as "a meningeal complication after pneumonia"

*Personal History*—The patient had always enjoyed good health, never had any serious illness, but had been subject to rather severe asthmatic attacks with spasms of coughing and expectoration, but never any hemoptysis

The most striking feature of the boy's past was his rapid development, both physical and mental He had always been athletic and very fond of outdoor sports, and excelled in competitions with other boys at school In June, 1912, he weighed 72 pounds, and in June, 1913, this had increased to 112 pounds (a gain of 40 pounds in one year) A year previously, or when he was 11 years old, his mother noticed that his voice was changing His mental development had been very noticeable, as exemplified by a more mature mental attitude shown by thoughtfulness and in other ways

*Present Illness*—In September, 1913, he had left home for his boarding school in perfect physical condition October 14 he had an acute exacerbation of his bronchial asthma and four days later was taken home At this time he had a profuse, foul smelling, greenish nasal discharge This attack, which was accompanied by more or less frontal headache, lasted three weeks, and there was deafness in both ears which persisted for a few weeks

October 21 the father was struck by the boy's widely-dilated pupils and a strange, staring expression of his face Since then the pupils had been unequal, sometimes the right being larger and at other times the left

Headache was present from the middle of October At the outset of the trouble there had been occasional attacks of nausea and vomiting and these increased in frequency up to the time of admission

At times during November and December he complained of transient blurring of vision Two weeks before admission his fundi and visual fields were examined by a competent ophthalmologist and found to be normal

During the first ten days of December there was a definite polyuria—four quarts in twenty-four hours on one occasion. Examination showed merely a low specific gravity, sugar was never found. A cranial roentgenogram was negative. The blood showed 16 per cent of eosinophils.

For six weeks before admission his temperature was subnormal. Vertigo was present during the previous week. Two days before coming to the hospital there was the first indication of diplopia.

*Physical Examination*—A lean, fine looking boy of 12 years, evidently large for his age, height, 5 ft 3 in, weight, 97 pounds—17 pounds less than at the outset of the trouble, skin showed a brownish pigmentation or discoloration, possibly due to exposure to the sun, long bones noticeably large, especially at their lower ends, external genitalia overdeveloped for the age of the patient, pubic and axillary hair present, abundant “down” on face.

Neck slightly but definitely stiff, some occipital tenderness, Kernig’s sign markedly positive on both sides, slight conjunctivitis.

*Neurological* Left pupil larger than right, both react to light and accommodation, diplopia present on looking to right, but not to left, movements of globes not well coordinated, fundi showed swelling of 2½ D on right and 1½ D on left, marked venous engorgement and tortuosity with slight embedding of vessels at disk margins.

Tests for the other cranial nerves showed an impaired olfactory sense and a slight deviation of the tongue to the left.

The Romberg was suggestive, with a good deal of swaying from side to side, but the patient was weak and had been confined to bed for several weeks. There was a tendency to stagger to the right when walking, and definite ataxia of left arm, as shown by finger tests.

Roentgen-ray examination of the head was negative, with normal sella, urine and stool examinations negative. Repeated examinations of the sputum showed no acid-fast organisms, tuberculin and Wassermann reactions negative, blood pressure and hemoglobin normal, differential white count showed 9 per cent eosinophils.

*Subsequent Notes*—December 26, lumbar puncture and withdrawal of 40 c c of a straw colored, cloudy fluid. The cell count showed 1,011 old, disintegrating, red cells (no fresh blood contamination) and eighty-five white cells per c mm, Fehling’s test positive, Noguchi test positive, no acid-fast organisms found.

December 27 Examination of the fundi showed elevation of 3 D right and 2½ D left, faint linear hemorrhages noted, and venous engorgement more marked.

December 28 Von Pirquet reaction negative, attack of numbness of right hand, arm, and right side of body, accompanied by motor aphasia.

December 30 Temperature subnormal since December 23, Wassermann reaction of spinal fluid negative.

January 1 The patient remained in the hospital only ten days and during this time his condition did not change essentially. He was discharged on this date. The diagnosis was uncertain. The possibility of tuberculous meningitis and brain tumor was discussed. Decompression was advised and refused.

After his stay in the hospital the patient was removed to his home in the country where he became progressively worse and had occasional periods of deep somnolence. He complained of no pain. The Kernig remained positive.

*Subsequent History*—January 28 he complained of numbness of the right hand and had a right sided convulsion. He remained practically comatose and was readmitted to the hospital, where an examination of the fundi showed an elevation of 5 to 6 D on both sides. The rigidity of the neck was increased, reflexes not elicited at knee, ankle or elbow, plantar response questionable, persistent weakness of right and possibly both abductores, a Kernig sign at 90 degrees persisted.

In order to determine the presence or absence of hydrocephalus, a diagnostic ventricular puncture was performed under local anesthesia. The needle was inserted to a depth of only  $2\frac{1}{2}$  cm. at Kocher's point and entered a dilated ventricular cavity. Fifty or 60 c.c. of yellowish fluid, such as was previously removed from the lumbar region, was withdrawn, examination of which showed 561 old red cells per cmm. (no fresh blood), 17 lymphocytes, Fehling's test positive.

The patient seemed to improve temporarily after the tapping, took nourishment and responded to stimuli, but suddenly, three hours later, the respirations became shallow and he rapidly failed.

*Comment*—At the outset, the symptoms of headache, nausea and vomiting, vertigo and blurred vision, and the physical signs of choked disk and diplopia made one think at once of an intracranial new growth. This idea was furthered later by the right-sided convulsion, which was followed by numbness of the right arm and leg, accompanied by aphasia. The rapidly increasing elevation of the optic disks also made it especially hard to rule out brain tumor. However, on careful examination of all the evidence, other factors appeared to play an even greater part in the syndrome and to cause the balance to swing over to the diagnosis of a probable infectious process, possibly similar to that from which his brother had died.

There was the history of a chronic nasal catarrh with an acute exacerbation a few weeks before the onset of the illness, followed by a transient deafness in both ears lasting two weeks. Then the cervical rigidity, positive Kernig's sign, and a beginning conjunctivitis was suggestive. Adding to this the peculiar character of the spinal fluid, its high count of mononuclear cells without any polymorphonuclear elements, and positive globulin and Fehling's tests, it seemed likely that we had to deal with a tuberculous meningitis. The symptoms of general pressure were by no means against such a diagnosis, nor were the variable pupillary and other phenomena associated with the cranial nerves. Two points, however, could not be overlooked in making a tuberculous lesion responsible for the condition, namely, the negative von Pirquet test and the negative examination of the lungs. The report on guinea-pigs inoculated with the patient's spinal fluid was not available at the time of his first discharge. Furthermore, no tubercle bacilli were found in smears of the spinal fluid or in the sputum.

In view of the necropsy findings, we must now consider a number of points which were not sufficiently noted in the presence of other symptoms which seemed to hold the forefront of the picture. The boy was very perceptibly overgrown, a fact noted by Dr. Pratt when referring him to the hospital. At the age of 12 years he measured 5 ft. 3 in. in height and two months before his illness weighed 114 pounds. A year previously his mother had noticed the change in voice to that of the adult masculine type. His father, too, had recently noted

a more mature mental attitude of thought and action. On examination the well developed, athletic figure was apparent. The brownish pigmentation of the skin was put down, at first, as due to exposure to the sun, but on more careful scrutiny the distribution of this coloring was not that usually seen in persons so exposed. The external genitalia were fully developed and there was abundant pubic and axillary hair, as well as an adolescent beard on the chin. These facts are of course very significant when one is acquainted with the intracranial post-mortem examination, but before death it was very easy to attribute the physical overdevelopment to the boy's athletic nature and participation in outdoor sports.

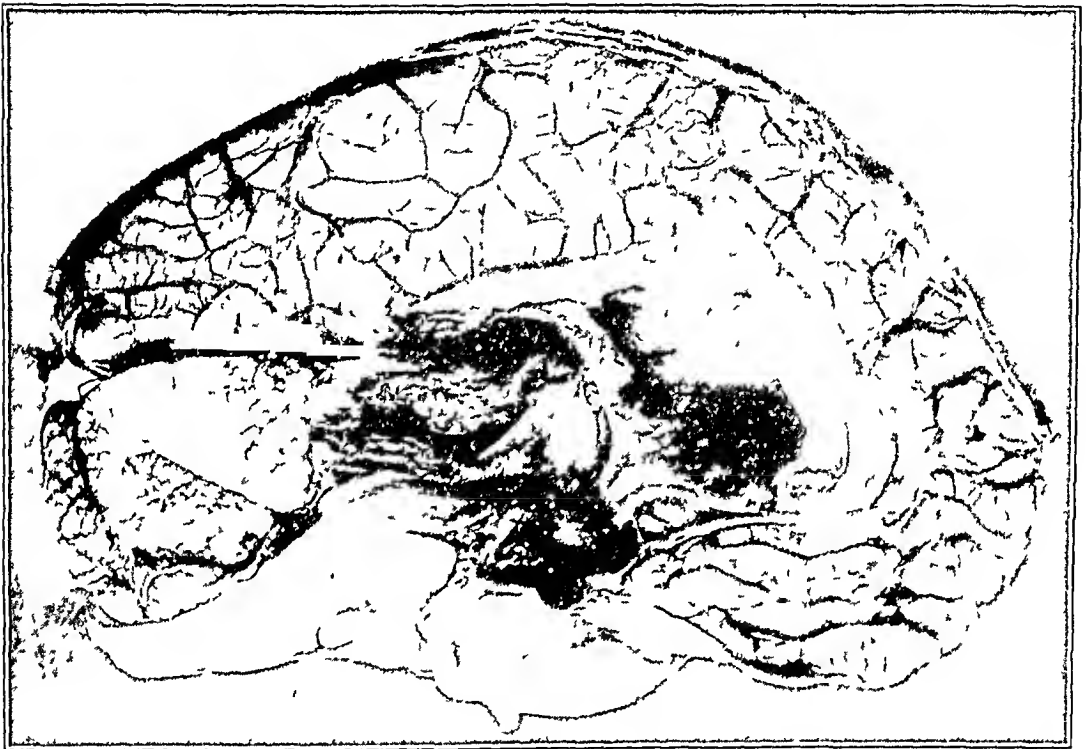


Fig 4—Case 3 Median section of brain showing tumor of the pineal region with implantation in floor of third ventricle, also secondary ventricular dilatation

In the words of Frankl-Hochwart, "When one finds in a very young individual (boy), along with the general symptoms of tumor, as well as the local signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development, and finally intellectual maturity, one must think of pineal tumor." We had before us a similar picture, obscured though it was by other factors.

One feature of the pineal syndrome was lacking, namely, the adiposity which has been dwelt on by most writers on this subject. In regard to this condition, which may be consequent on or associated with



disturbed functions of the pineal gland, there are, at present, three views first, that of Marburg, that obesity is one of the expressions of overfunctioning of the gland, hyperpinealism, second, the view held by other authors, namely, that it may be due to a pineal tumor supposedly causing a lessened functioning of the gland, hypopinealism, and third, the view that the adiposity is due to secondary changes in the hypophysis brought about by the pressure excited by internal hydrocephalus (Cushing<sup>11</sup>)

So far, Marburg's case of so-called hyperpinealism, with its accompanying adiposity, is the only one attributed to glandular overactivity, and, as Kidd says,

Even absence of any recognizable histological changes in the pituitary or other glands in such cases does not exclude the possibility of associated dis-pituitarism due to subtle metabolic or chemical changes of which, at present, we have no knowledge. Then again, adiposity occurs in so many other conditions and its modes of production are still so obscure, that we must conclude, I think, that it is uncertain whether hyperpinealism in man ever causes adiposity per se

Of the sixty cases of pineal tumor collected by Bailey and Jelliffe<sup>2</sup> in 1911, fourteen are recorded as being associated with adiposity to a greater or less degree. Marburg's case is included in this series. The hypophysis was examined in very few of these cases, so it cannot, as the authors state, be shown by statistics what relation this organ may have borne to the syndrome. There is in all cases, however, a marked degree of internal hydrocephalus, and this factor may well disturb the functioning of the pituitary even though the cells of the latter remain histologically normal.

*Xanthochromia*—Mention has been made of the peculiar color and characteristics of the spinal fluid in the case under consideration, obtained both by lumbar puncture and by tapping of the lateral ventricle. Such a condition of the cerebrospinal fluid has been termed xanthochromia and is usually associated with an increase in the cellular and albuminous elements of the fluid, particularly fibrinogen, these substances causing the production of the so-called "massive coagulation." Several cases showing this condition were collected by From<sup>21</sup> in 1903, and since then a number of others have been reported.

A lesion which causes a constriction or compression of the meninges around the cord, thus making the subarachnoid space in the lumbar region a closed cavity is likely to produce such a condition of the fluid. Such lesions have been associated with meningomyelitis, tuberculous meningitis, Landry's paralysis, tumors of the cord, and, rarely, cerebrospinal lues.

Into a closed cavity of this sort the elements necessary to the production of "massive coagulation and xanthochromia" could come in

two ways, (1) by transudation or (2) by capillary hemorrhage. The exudative lesions like myelitis and meningitis easily account for the products accumulated through transudation, and this process is no doubt the most usual one. The origin of the capillary hemorrhages is not so clear, but in the few cases reported they have been associated with tumor of the cord.

In view of these facts, Mestrezat<sup>48</sup> concludes that the physical and chemical properties of the cerebrospinal fluid, together with the clinical and necropsy findings, demonstrate the reality of a closed cavity and the existence of stasis of the fluid as necessary to the production of the syndrome.

In cases of xanthochromia previously reported, the fluid has always been obtained by lumbar puncture. In our patient, the fluid taken from the ventricle was identical with that previously procured from the lumbar region. Its color and cellular content corresponded with the other cases reported. Massive coagulation, however, did not exist, although albumin was present to a definite degree, as shown by the Noguchi test.

Many tumors which grow into the ventricles are accompanied by xanthochromia due, doubtless, to the escape of blood cells from the surface of the tumor into the fluid. We have seen a number of examples in this clinic.

#### PATHOLOGY

A study of the diseases to which the pineal body is subject has been confined almost exclusively to the different varieties of tumors which have been found to arise either from the gland itself or from those structures which lie in its immediate neighborhood and therefore involve the pineal secondarily. Very rarely conditions other than tumor have been mentioned in connection with pineal pathology, but these play an inconspicuous and perhaps dubious part in this chapter of the study of the gland.

Cysts seem to be the most common and earliest recognized of the tumors of the pineal, a "hydrops cysticus" of this organ having been described by Virchow<sup>77</sup> in 1863. Marburg in 1909<sup>40</sup> gave an excellent description of the types of pineal cysts. These he divides into two classes: (1) involution, formed by the degeneration of areas of pineal substance due to sclerosis of the blood vessels, and (2) retention, arising from the "recessus pinealis," and lined by ependyma, by which they are distinguished from the involution type.

Next in point of frequency come the teratoma, for a classical description of which all authors refer back to Weigert's article<sup>79</sup> of 1875. In brief, the main facts which have been assembled regarding this type of pineal tumor are as follows. They occur almost exclusively

in children, Neumann's patient of 27 being the only exception<sup>51</sup> All others were under 15 years of age The tumor occurs always in the anterior portion of the pineal, and this fact has led some authors, notably Askanazy,<sup>1</sup> to ascribe their origin to the anlage of the parietal eye of the lower vertebrates Marburg confirms this theory by his discovery of the remains of the "nervus parietalis and ganglion parietale" in the most anterior part of the pineal in the neighborhood of the taenia habenulae The elements contained in these tumors are the usual ones found in the teratomas of other organs, namely, hair, cartilage, sebaceous glands, smooth muscle fibers, fatty tissue and occa-

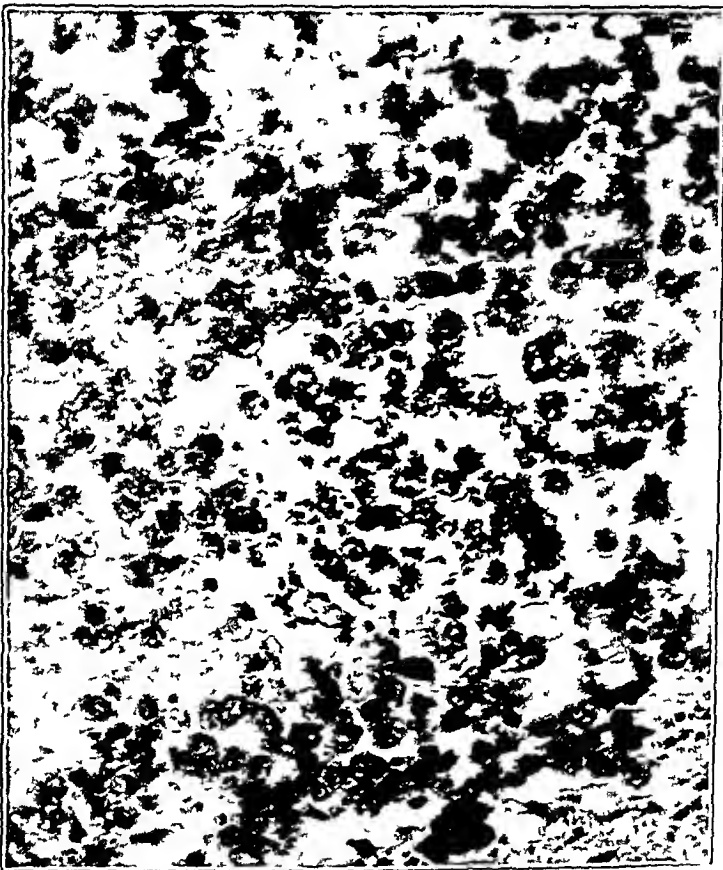


Fig 5—Showing character of cell masses (Mag  $\times 250$ )

sionally axis cylinders The cases of teratoma on record are those described by Weigert, Coats,<sup>10</sup> Falkson,<sup>16</sup> Ogle<sup>57</sup> (two cases), Gauderer,<sup>23</sup> Gutzeit,<sup>26</sup> P Neumann, Hueter,<sup>31</sup> Frankl-Hochwart,<sup>19</sup> and Bailey and Jelhffe<sup>2</sup>

A great deal of discussion arises as to whether or not the other recorded types of tumor are distinct enough to be classified separately Marburg groups all tumors of the pineal other than cysts and teratomas into a general class of "mixed tumors," and there is undoubtedly much to be said in behalf of this method From a general survey of the cases

described, however, it seems probable that four other fairly distinct varieties may be recognized, namely, (1) gliomas (in the cases of Duffin,<sup>13</sup> Schultz,<sup>68</sup> Lawrence,<sup>38</sup> Nothnagel's second case,<sup>54</sup> and Raymond and Claude<sup>61</sup>), (2) sarcomas (Gowers,<sup>25</sup> Kny,<sup>36</sup> M Neumann's second case, Nothnagel's first case, Pontoppidan,<sup>60</sup> Feilschenfeld,<sup>17</sup> and Hosslin<sup>32</sup>), (3) carcinomas (Massot,<sup>42</sup> Daly,<sup>12</sup> Forster,<sup>18</sup> and Hempel<sup>29</sup>), (4) psammoma (Friedreich,<sup>20</sup> Blanquinque<sup>6</sup> and possibly Wernicke<sup>80</sup>) From a histological standpoint there is no reason why pure tumors of these four distinct types should not arise from the pineal. The four types of mother cells which produce them



Fig 6—Showing character of cells with irregular chromatin and nuclear figures (Mag  $\times 1,000$ )

are a constant anatomical element of the gland, and there is no basis for questioning the pathological diagnoses made, at least by the later authors

That there is, however, a large class of pineal tumors which cannot be put down as conforming on the whole to any one specific type, is likewise true. For the present, therefore, it would seem best to follow Marburg and assemble these under the heading of "mixed tumors." In this group possibly belong the angiosarcoma of Hart,<sup>27</sup> the gliosarcomas of Howell's three cases,<sup>33</sup> and that of Zenner,<sup>82</sup> the neuro-

glioma of M. Neumann's first case,<sup>50</sup> the psammomas of König,<sup>37</sup> and Oestreich and Slawyk,<sup>50</sup> the chorio-epitheliomas of Askanazy<sup>1</sup> and of Goldzeiger,<sup>34</sup> the unclassified tumors of Blane,<sup>5</sup> Schmidt,<sup>67</sup> Schearer,<sup>65</sup> and Schmid,<sup>66</sup> and the "mixed tumors" of Marburg and of Pappenheimer.<sup>58</sup> Possibly we should put the adenoma described by Meyer,<sup>44</sup> and the epithelioma described by Estèves and Beatti<sup>15</sup> in this larger class also.

Turning now to the extremely rare instances of disease of the pineal, other than tumors, we find hemorrhage described twice (Simon,<sup>70</sup> Zeigler<sup>83</sup>), abscess once (Birsch-Hirschfeld, quoted by Marburg), and syphilis once (Lord<sup>30</sup>), while Pontoppidan was unable to make an exact diagnosis in his case between syphilis and sarcoma.

*Pathological Report*—The postmortem studies in our own case are as follows. An examination of the head only was permitted after death. This limited necropsy was performed by Professor Councilman five hours later. His description of the findings is as follows:

The brain has been removed and bisected longitudinally (Fig. 4). The ventricles are dilated. In the posterior half of the lateral ventricle, in the region between the tail of the corpus callosum which is elevated, and the medulla, in the region of the pineal gland, there is a tumor mass 5 cm long, extending from the anterior edge of the cerebellum to within 4 mm of the foramen, for a distance of 4.6 cm. Between the medulla and the corpus callosum the tumor measures 2.5 cm. In the center of the tumor mass is a large blood clot. The tumor seems to be composed of a soft very much congested material, probably in part hemorrhage. It is adherent to the structures below it. In the floor of the greatly dilated third ventricle, which measures 2.5 cm antero-posteriorly, there is a similar mass of tumor tissue, 2 by 2 cm, in no way connected with the primary tumor tissue. This is evidently an intraventricular implantation of the primary tumor.

*Microscopical Examination*—Various parts of the tumor and its ventricular implantation show essentially the same structure. It is composed (Figs. 5 and 6) of loosely placed cells of an epithelial character without any very definite arrangement. They have large nuclei and a small amount of pale cytoplasm. There is no definite stroma. Between the cell masses, in places there is abundant hemorrhage, and in others great numbers of cells of the lymphoid type. The appearance resembles the cellular tumors of the hypophysis, in the nuclei are large amounts of chromatin and granules. At one place, taken from the lower aspect of the tumor, there is a small amount of adherent choroid plexus which shows very slight reactive new growth. The implanted fragment of the tumor shows some invasion of the pituitary body by the growth (Fig. 7). Degenerative processes in the tumor are common, there being comparatively large areas composed of necrotic cells. Various cell types other than the usual are encountered, around them are giant cells with peripheral nuclei with division figures, of normal type, in the single nuclei. Nuclear figures in small numbers are found in nearly every cell. Most of the epithelial cells of the tumor take the hematoxylin stains very intensively, they all seem to be of about the same type. There are no concretions in the tissue.

*Diagnosis*—Struma of the pineal gland.

*Comment*—The tumor mass on the surface of the third ventricle is not to be regarded as a metastasis, but as a surface implantation.

due to single cells or portions of the tumor which, having become detached, have formed a junction with the surface of the ventricle, the extension here being of the same character as the tumor implantations which only occur on the peritoneal surface

That the tumor was one of very rapid growth is shown by the many nuclear figures and evidences of indirect division, and yet there was no tendency to invasion except in the case of the hypophysis (Fig 7) The character of the cells here corresponded to that noted elsewhere, but the supporting stroma was more evident, owing to the

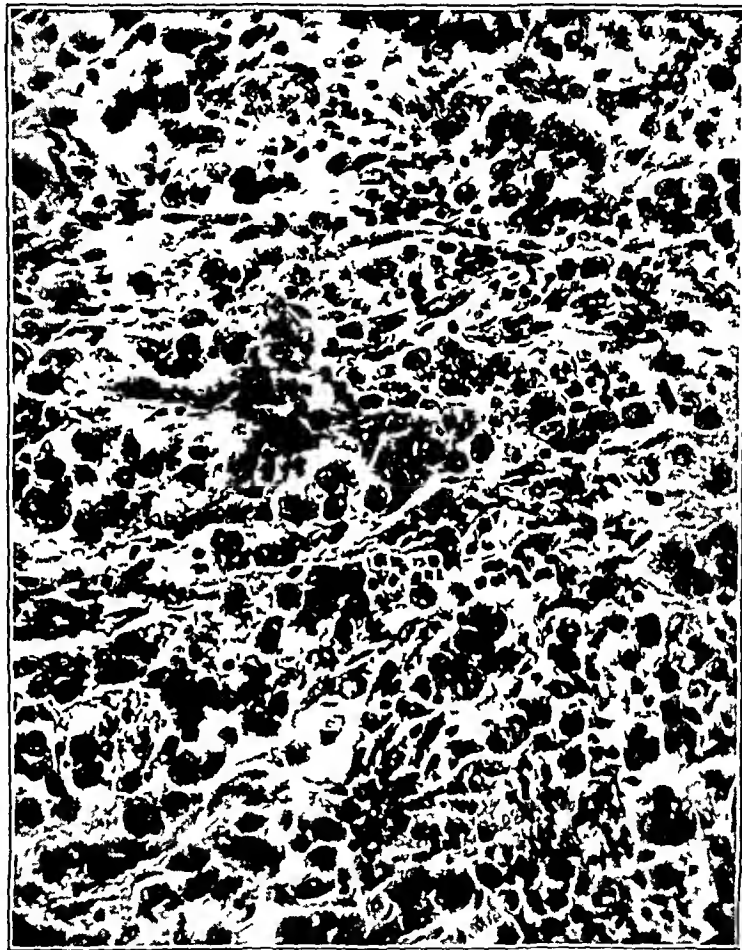


Fig 7—Showing invasion of anterior lobe of the pituitary body by tumor (Mag  $\times 250$ )

difference in structure of the tissue invaded, and the resulting appearance was more like that of a carcinoma

A striking feature of the tumor as a whole was the great number of lymphoid cells it contained. These were present both in large masses grouped together, and also as scattered elements throughout the growth without definite arrangement. This enormous development of lymphoid tissue in a patient 12 years of age brings out the possibility of associated lesions elsewhere in the body, especially in connection

with the thymus and lymph glands. The limited necropsy prevented studies of these tissues.

The question whether such a tumor represents an overfunctioning or an underfunctioning of the gland cannot be decided definitely on the basis of the anatomical findings. The structure corresponded in many respects to the diffuse struma often seen in the pituitary and which usually accompanies states of pituitary insufficiency. It is difficult to tell from the histological appearance alone of a ductless gland whether or not this is functionally overactive or underactive, though in the case of the thyroid we assume that we can do so, and possibly we may also in the pituitary gland. If this particular struma of the pineal which we are considering represents functionally overactive cells, the symptoms would be explained as Marburg has explained them on the basis of hyperpinealism, and the experimental feeding observations by Dana and McCord might be interpreted as lending support to such a view. Two points, however, render such a view improbable. In the first place, the cells show an extreme rapidity of growth, indicating an active formative faculty which is usually associated with a loss of specific function. Further, the cytoplasm of the cells contains no demonstrable granules, and these are usually regarded as representing functional activity.

It is our impression, from what we know of the physiology of the normal gland, as well as from the results of Foa's and our own experimental observations, that sexual ripening occurs when the pineal ceases to be functionally active, or when it is removed, and on this basis we incline to the belief that the tumor in most of these clinical cases is associated with an inhibition of the normal products of pineal secretion. If this were really the case, however, one would suppose that glandular feeding would postpone adolescence, but from the observations of Dana and McCord the reverse seems to occur. Our own studies in this direction with the feeding of young guinea-pigs and rats were not conclusive and it is a matter which deserves further study.

#### SUMMARY

1 Extirpation of the pineal in young chickens and lower animals tends to hasten normal maturity.

2 Tumors of the pineal gland in children occurring before the age of puberty usually give rise to a syndrome characterized by precocious adolescence.

3 Feeding the gland substance to young animals is said to have the same effect as extirpation, but the observations are somewhat inconclusive.

4 A report of three cases of supposed pineal tumor, one of which was certified by necropsy, is offered as a further contribution to the study of this gland

I take this opportunity of expressing to Dr Harvey Cushing my deep gratitude for the help, both by suggestion and inspiration, with which he has guided this work, and for his kind permission to publish the cases from his clinic I also wish to thank Dr W T Councilman for his advice and cooperation concerning the pathological features of the paper

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# THE ADJUSTMENT OF PRESSURES IN INDUCED PNEUMOTHORAX

WITH ESPECIAL REGARD TO THE MOBILITY OF THE MEDIASTINUM AS INDICATED BY THE MANOMETER \*

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GRAVINGHURST, ONT

During the treatment of phthisis by compression of the lung, there is need of exercising a nice judgment regarding the degree of pressure that should be maintained throughout a long series of injections. Our experience is that the displacement of the mediastinum is of first importance in the adjustment of pressure at any time, and our purpose is to show how this may be estimated with fair accuracy by the aid of the manometer and without the help of the Roentgen ray when the result of physical examination is uncertain.

The first consideration is to obtain a satisfactory collapse of the diseased lung, but while one is trying to effect this a compromise in the pressure desired may have to be made for the safety of the less diseased lung and of the heart. Cases in which collapse of the lung takes place easily seem rarely to suffer strain to either organ if the collapse is gradually induced, and these are the cases in which the mediastinum will usually be found movable.

The cases in which collapse of the lung is more difficult, unless this difficulty is due solely to an induration of the lung, will, because of thickening of the pleura and adhesions, have a much less easily displaced mediastinum. This relative rigidity of the mediastinum then becomes a great protection to the very cases that require considerable pressure to reduce the size of the lung. With lateral adhesions in the upper part of the thorax, a marked displacement of the mediastinum may nevertheless take place.

The effect that the extra work will have on the functioning lung is a source of continual anxiety. The beneficial influences, which according to accepted theories account for its improvement, may be sufficient to arrest progress of disease or render it quiescent, but during the long course of treatment indolent progress may be noted after earlier marked improvement. This lung becomes enlarged, emphysematous and elongated. Lord<sup>1</sup> considers the arguments in favor of the

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<sup>1</sup> Lord. Diseases of Bronchi, Lungs and Pleura, 1915, p 584

beneficial influence of the overwork of the better lung as invalid Aron<sup>2</sup> sees little chance for healing of disease in the better lung because of its greater respiratory movement and finds it impossible to imagine that the better lung can heal under such conditions. There is such danger to a diseased lung from the greater excursion that he urges that on no account should compression be pushed so far that breathing is stopped entirely in the compressed lung. The type of respiration becomes modified as is best suited to the need of the individual at any one time (Brown<sup>3</sup>) and Aron<sup>2</sup> finds in man that the untreated lung breathes with increasing depth the more the treated lung is excluded from respiration, as is shown by greater fluctuations of a manometer connected with the pleural cavity of the functioning lung. Aron's<sup>4</sup> experiments on animals show the concurrent changes of pressure in the pleura of the functioning side while one lung is gradually excluded from respiration. After a mean pressure of zero has been reached the depth of respiration which, following an initial increase, has steadily lessened and has been compensated by increased frequency of respiration, promptly increases with lessened frequency of breathing, and at the same time there is a very marked rise in blood pressure. The lessening depth of respiration of the functioning lung is shown in the pleural cavity by the negative pressure's becoming less marked on inspiration and more marked on expiration, thus showing a decreased amplitude.

There may be embarrassment to the circulation with either fixed or movable mediastinum, since, on the one hand, rigidity may cause pressure to be brought to bear on the heart, vessels and nerves, and, on the other hand, flexibility will permit varying tension, kinking, strain and pressure as well.

The right heart, besides the handicap of diminished vascular area in the collapsed or compressed lung and the loss in part of the pump action of the thorax, has to undertake the maintenance of an increased circulation in the functioning lung, and is further embarrassed by more or less lateral displacement (sometimes with a twist on either vertical or horizontal axis or both), and the pressure of the relatively unyielding gas cavity. Moreover, the heart is the first to feel the effect of diminished oxygenation, and the general need of oxygen also causes a rise in pressure in the systemic circulation. Pressure or strain on nerves may also affect the innervation. The fact that the right heart hypertrophies in man as well as in animal experiments, has been shown at necropsy, but it has also been shown that it sometimes fails to do so. Improvement in the heart's action through lessened toxemia and

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2 Aron. Berl klin Wchnschr., 1913, L, 305

3 Brown, T. R. Modern Medicine, Osler and McCrae, 1907, iii, 549

4 Aron. Virchows Arch f path Anat, 1896, cxlv

improved general condition more than make up for these embarrassments in favorable cases. The heart also may benefit by being enabled to return to a more normal position after previous great displacement due to a contracted lung.

As to a satisfactory collapse of the diseased lung, various writers set different ideals of attainment, though all aim at the exclusion, if possible, of the treated lung from respiration. Saugman and Hansen,<sup>5</sup> while approving Foralini's objective of compression as a curative measure, were able to obtain complete compression in only 15 per cent of their cases. On the other hand, Dunham and Rockhill,<sup>6</sup> using the operation as a palliative measure and controlling their work with the Roentgen ray, found that refilling should be frequent and the gas pressure slight, the amount of gas injected being just sufficient to keep the lung collapsed and no more, a zero inspiratory pressure being more than enough. Brauer and Spengler<sup>7</sup> emphasize the general rule that the better and larger the pneumothorax obtained the less need be the pressure, and they consider the object of the operation has been reached as soon as there is no negative inspiratory pressure. When the lung is not too dense, a pressure of 2 to 4 cm of water is considered by various writers to be sufficient to keep the lung compressed if there are no adhesions. This pressure, if well borne, may be increased to 7 to 8 cm. If adhesions remain, possibly 40 cm may be necessary (Rist<sup>8</sup>). Saugman has maintained a pressure of 20 to 30 cm of water for months, but has never exceeded 8 cm of mercury (108.8 cm H<sub>2</sub>O), while Brauer's limit has been 4.5 cm Hg. Davies<sup>9</sup> considers it useless to persevere in the separation of adhesions when a pressure greater than 1 cm Hg (13.6 cm H<sub>2</sub>O) is necessary.

Exclusion of the lung from respiration becomes from the standpoint of practice, a relative matter, since the frequency of refills necessary to maintain a consistent pressure is scarcely practicable, and in the intervals considerable reexpansion may take place. When the pneumothorax is established, an optimum point of pressure is usually found for each individual, determined for him mainly by the degree of tension the mediastinum will bear.

It has been shown by experiment that those animals bear pneumothorax best in which the elasticity of the mediastinum best resists displacement (Bruns<sup>10</sup>). The mediastinum is strengthened also by the deposit of fat. Man is fortunate in having a mediastinum with fair

5 Saugman and Hansen. Beitr z Klin d Tuberk, 1910, xv, 303.

6 Dunham and Rockhill. Jour Am Med Assn, 1913, lxi, 826.

7 Brauer and Spengler. Beitr z Klin d Tuberk, 1909, xiv, 419.

8 Rist. Quart Jour Med, 1913, vi, 22.

9 Davies. Brit Med Jour, April 25, 1914, No 2782, p 897.

10 Bruns. Beitr z Klin d Tuberk, 1909, xii, 1.

elastic tension because of the relatively small distance between the heart and the sternum. However, at the site of the atrophied thymus there is a weak area which extends from the second to the fourth cartilage and may be 3 or 4 cm deep, filled with loose connective tissue and fat. Another area where the pleura of the right side is relatively unsupported lies between the aorta and esophagus between the fifth and twelfth vertebrae (Nitsch<sup>11</sup>). At these situations the pleurae are capable of further distention after a certain pressure, which first causes a general displacement of the mediastinum, has been passed. There are apparently great individual differences in the resistance of the pleurae to pressure. A healthy pleura will bear a considerable positive pressure from inflation without causing dyspnea. A recently inflamed pleura becomes relaxed and yields more readily to pressure than the normal pleura, while more chronic intrathoracic inflammation and thickening increase the resistance. Pressure is found to be borne with less dyspnea when the pleura is thickened than when it is thin. This may be seen in pleural effusion, which, when recent and with a lower pressure, produces greater dyspnea than when the pleura is thickened and the pressure is higher.

For determining the pressure that will be the best compromise for the individual case, it is, therefore, important to take into consideration the degree of movability or rigidity of the mediastinum. The index of this is the position of the heart which it may or may not be possible to locate accurately by physical examination. The Roentgen ray is not always available, or it may be impossible to use it at every seance, but without changing the position of the patient the manometer gives information as to mediastinal displacement which serves as a guide at every refill. Naturally, information will be incomplete during the earlier inflations, at least until the zero point has been approached.

Von Muralt,<sup>12</sup> and Hamman and Sloan,<sup>13</sup> also, state that the manometer may indicate a too movable or too rigid mediastinum. Their views, however, are completely at variance. Von Muralt says that other things being equal, a flexible mediastinum is shown by a rapid rise in pressure with a small respiratory movement of the fluid in the manometer, a rigid mediastinum by a slow rise in pressure with large respiratory movement of the fluid. Hamman and Sloan hold that a slow increase in pressure with wide respiratory variation, indicates a flexible mediastinum, a rapid increase in pressure with small respiratory variations, a rigid mediastinum.

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11 Nitsch. Beitr. z. Klin. d. Tuberk., 1911, xvm, 359.

12 Von Muralt. Beitr. z. Klin. d. Tuberk., 1911, xviii, 359.

13 Hamman and Sloan. Bull. Johns Hopkins Hosp., 1913, xxiv, 53.

Contrary to these writers we<sup>14</sup> have found that a flexible mediastinum is shown by a slow rise in pressure with relatively small amplitude of movement of the fluid in the manometer on breathing, and a rigid mediastinum by a more rapid rise in pressure with relatively large amplitude. The slow rise in pressure when the mediastinum is unduly flexible is so obvious that it seems probable that von Muralt has not correctly stated his position. In his paper some ambiguity of the context suggests that this is so. Moreover, with a flexible mediastinum there are frequently to be noticed certain relatively stationary points at which there is no further rise of pressure after one, or even two, deciliters of gas have been introduced. These points are most frequently noticed when the mean pressure is near zero. The oscillations are also sluggish when the mediastinum is movable. When the mediastinum is more rigid the stationary points are not in evidence and the movement of the fluid in the manometer is more abrupt. These observations, recorded in an earlier paper, are in accord with the following theoretical considerations.

The position of the mediastinum at any time is accepted as one of equipoise between varying tensions of the two pleural cavities, the resultants of several factors, chiefly the elasticities of the lungs (West<sup>15</sup>). When the tension of one pleural cavity is lessened "the heart, the most delicate index of a change of tension on either side," will move towards the side on which the intrapleural tension is greater, i. e., on which the negative pressure is more marked, "pushed in that direction by a force equal to the differences of those in the two pleural cavities" (Emerson<sup>16</sup>). In expiration, with a general relaxation of the thoracic wall and diaphragm, this position of equilibrium of the mediastinum necessarily exists, and during quiet respiration the same condition obtains, since the central tendon of the diaphragm does not stir. During more active inspiratory movement, however, modifying forces come into play so that the position of the mediastinum becomes a resultant of the antagonistic intrapleural tensions and the tension put on the mediastinum by the combined influence of the descent of the diaphragm and deepening of the thorax. The entrance of gas into one pleural cavity will, however, relax the diaphragm on that side and its dome will become lowered. This permits the mediastinum to yield itself the more readily to satisfy the variable tensions of the two pleural cavities. Irrespective of prevailing intrapleural tensions, inspiration will have the effect of flattening the curves, so to speak, of the irregular mass forming the mediastinum. This would even be

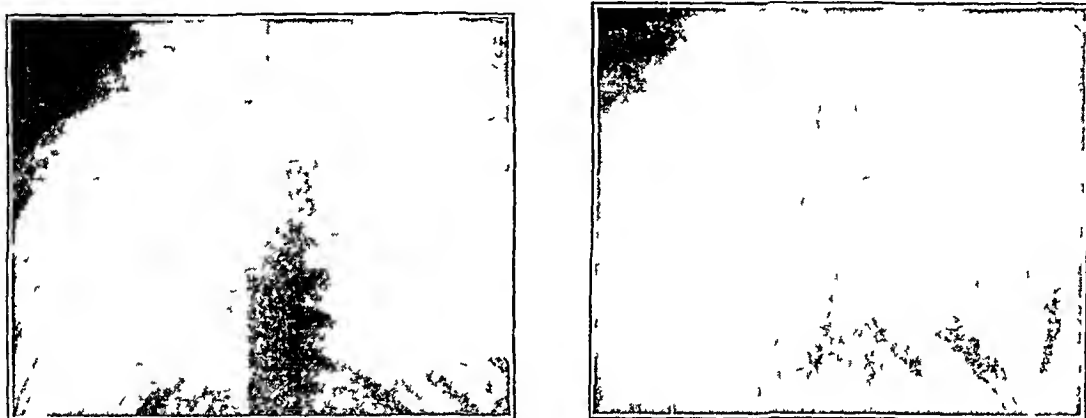
14 Parfitt and Crombie. *Canad Med Assn Jour*, 1915, v, 373, 489.

15 West. *Intrapleural Tension*, *System of Medicine*, Allbutt and Rolleston, 1909, v.

16 Emerson. *Johns Hopkins Hosp Rep*, 1903, xi.

the case in an open elastic cage with bulging central partition if the anteroposterior and vertical diameters were enlarged. This stretching with flattening of the bulge of the mediastinum on inspiration becomes of great importance in open pneumothorax as an aid to the respiration of the sound lung, as pointed out by Sehrwald<sup>17</sup>. Thereby a greater intrapleural tension is created on the sound side which is a necessary factor for its increased respiration.

The differences of tension between the pleural cavities while a closed pneumothorax is being induced is shown in the tables of Aron's<sup>4</sup> experiments. Though these were obtained in animals, analogous results would be expected in man. As might be anticipated, the actual differences in tension between the two cavities at each phase of respiration shows a constant increase in tension in favor of the



Figs 1 and 2—Fig 1 Full inspiration (Case 1) Fig 2 Full expiration (Case 1) Movable mediastinum, roentgenograms of chest taken the third day after the refill of April 3, 1915 (see Fig 3)

pleural cavity of the functioning lung. Except for a very short time early in the operation, this difference of tension is much greater on inspiration. If relative intrapleural tension alone adjusts the position of the mediastinum, it would at first sight seem that the mediastinum should move toward the sound side on inspiration and away from it on expiration. That the reverse movement obtains is shown by the fluoroscope and roentgenogram (Figs 1 and 2), and on inspiration the mediastinum is seen to move toward the pneumothorax cavity and away from it on expiration. The degree of this movement will necessarily depend on the relative mobility of the mediastinum. If flexible, the movement is much more marked when there is considerable gas in the cavity than when it is relatively empty. In the latter instance a more normal condition is approached, since the diaphragm is less

<sup>17</sup> Sehrwald *Deutsch med Wchnschr*, Aug 22, 1889, quoted by Emerson Note 16



relaxed, the intrapleural tension is increased and there is less necessity for a readjustment of the position of the mediastinum. The explanation of the movement of the mediastinum toward the pneumothorax cavity given by Bittorf,<sup>18</sup> and Saugman and Hansen,<sup>5</sup> also, is that the inspiratory increase of tension in the pneumothorax cavity causes the mediastinum to move toward that cavity. Because of the experiments just mentioned this explanation demands consideration, since there is a relatively greater tension on inspiration in the pleural cavity of the functioning lung. The enlarged thorax on expiration will, however, cause a shift of the mediastinum to the pneumothorax side through the altered intrathoracic pressure, modified, of course, by the restraining opposed tension of the sound pleural cavity. The values of the pressures recorded in the pleural cavity of the functioning side must be accepted with some reservation since on this side the force of cohesion is practically unimpaired and this force, according to Brauer<sup>19</sup> and Roth,<sup>20</sup> abolishes the negative pressure which becomes a fact only after a pneumothorax has arisen.

The mediastinum, then, in an artificial pneumothorax, plays an active part on inspiration, and a passive part on expiration, when its position is determined by the opposing intrapleural tensions.

Therefore, when the mediastinum is movable the inspiratory enlargement of the thoracic space on the side of the pneumothorax will be reduced by the encroachment of the mediastinum on it, which is made possible by the rush of air into the untreated lung, and this yielding of the inner wall of the cavity will in part neutralize the increased intrathoracic tension on the treated side. At the same time the partially collapsed lung will have occasion to expand less than if the inner wall were more rigid, and with the force of cohesion lost it is not in such good condition to expand as is the functioning lung. Because of its greater elasticity, the functioning lung will also yield more readily on expiration than will the partially collapsed lung, the mediastinum will move to that side and room will so be found for the gas cavity which will have its tension somewhat increased and pressure reduced by the greater tension of the sound pleura transmitted to it.

With the effect of inspiration and expiration on the gas in the pleural cavity partially neutralized by this swaying of the mediastinum, the pressures registered in the manometer will be less than if the full force of the expansion and contraction of the chest wall had obtained and the amplitude of movement of the fluid will consequently be less. (Note the especially small amplitude in Fig. 3.)

18 Bittorf *Munchen med Wchnschr*, June 7, 1910, No. 23, p. 1218

19 Brauer *Beitr z path Anat u z allg Path*, 1905, Seventh Sup., p. 762

20 Roth *Beitr z Klin d Tuberk*, 1905, iv, 437



because of varied conditions of breathing which best suit the patient's need at the moment Emerson<sup>10</sup> has shown that the chest may assume different sizes on the introduction of fluid while the intrathoracic tension remains approximately the same, and that the respiratory oscillations are not in direct proportion to the respiratory movements, the efficiency of which bears an inverse relation to the degree of distention.

In either case, also, the pressures will be modified by the degree of expansion of the treated lung and some confusion in interpretation may be caused. As pointed out by Hamman and Sloan,<sup>12</sup> a reexpanded lung is shown by a very gradual rise in pressure on introducing each deciliter of gas, while a lung that remains collapsed is shown by a

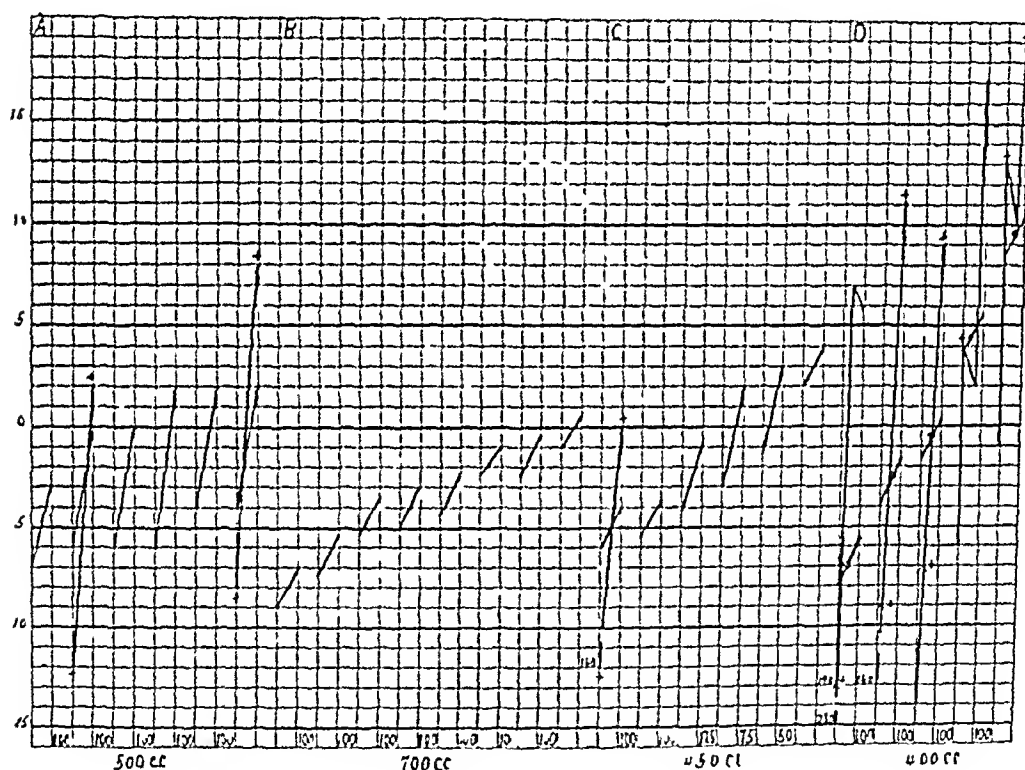


Fig 4—Case 2 Movable mediastinum becoming fixed A, second refill, Sept 23, 1914 Interval two days Bore of needle, 0.035 inch Heart's impulse displaced 3 cm to left by refill B, seventh refill Dec 8, 1914 Interval twenty-one days Bore of needle, 0.018 inch Heart's dulness displaced 5 cm to left by refill, hyperresonance 3 cm to left of midsternal line after refill C, ninth refill, Jan 30, 1915 Interval twenty days Same needle Heart's dulness before and after refill fixed at 25 cm from position noted before beginning of pneumothorax D, thirteenth refill, May 11, 1915 Interval twenty-eight days Same needle Heart's dulness fixed

slow rise at first and then a very sudden and marked rise. The stationary points already mentioned, at which the pressure fails to rise following the introduction of one or two consecutive deciliters of gas help, we think, to distinguish such conditions. (See A, C, D, Fig 3, and A and B, Fig 4) They are points of emphasis in the curve char-

acteristic of the slow rise of pressure found when the mediastinum is movable. They may perhaps be explained by a somewhat irregular and momentarily more marked satisfaction of the elasticity of the functioning lung, the gradual satisfaction of which mainly accounts for the relatively slow rise in pressure, made possible by the further yielding of the mediastinum, partly the result of the continued relaxation of the diaphragm, rather than by an enlargement of the pleural space caused by the irregular enlargement of the thoracic wall, or than by an irregular collapse of the treated lung. We may surmise that the weak areas described by Nitsch play some part in their causation, as it is not unusual for hyperresonance to extend markedly to either side of the sternum even without a positive intrapleural pressure. High levels of the stationary points which may have been caused by bulging of such weak areas, were found in a case of very large pneumothorax with extreme movability of the mediastinum. At any rate, stationary points are found in consecutive refills to be more or less constant at some one, or at several levels in the pressure curves in cases in which the mediastinum is readily displaced, and are not found in those in which it is relatively fixed (Figs 3 and 4).

The pressures for deep respiration, taken both at the beginning and the end of the refill, give information which is also suggestive and point to either condition, although the risk of rupture of the lung makes such deep breathing a dangerous experiment. With flexible mediastinum the amplitude for deep respiration is not disproportionate to that for quiet respiration (Figs 3 and 4A) and is about the same at the end of the refill as at the beginning. The incompletely collapsed lung no doubt plays a material part here as well as the yielding midwall. With rigid mediastinum, and especially if the rigidity of the pneumothorax wall is, so to speak, increased by a lung which does not readily reexpand, the amplitude may be quite disproportionate to that for quiet respiration, and extreme (Fig 4) both at the beginning and at the end of the refill. There may also be material differences in the amplitude before and after the inflation depending on the recompression of the lung and on the muscular power that is brought to bear. When a rigid mediastinum obtains and the amplitude for forced respiration is relatively small, it is probable that there is considerable lung excursion which compensates the respiratory movements.

Needles of relatively small bore are, we think, better adapted for the estimation of varying amplitudes of movement of the water column than larger needles. With the latter the slowly rising curve and the stationary points can be well shown only by determining the mean pressure, after the manner adopted by Saugman, by means of a valve on the rubber connection between the limbs of the manometer, or, by a valve on the tubing to the manometer, as has been suggested by me

The device recommended by v Adelung<sup>21</sup> for making mean readings by means of a bypass might be modified so as to give a suitable standard caliber for noting oscillations, and this would make one independent of variations in the bore of different needles. The pressures recorded through a small needle will lie in the upper half of the amplitude recorded by a large needle, i. e., near the true mean pressure shown with a large needle (Fig 3, C and D). Needles of a bore of 0.018 inch and 0.022 inch, B. W. G. Nos 26 and 24, have been used mainly. An amplitude of 2 cm. or less with a needle of 0.018 inch bore is suggestive of mediastinal displacement, and the more the excursion decreases or increases from this measurement the more or less suggestive it becomes.

We have also previously described a phenomenon, not infrequently found, which we have not seen mentioned elsewhere, but it is of some interest here. When the patient is asked to hold his breath at the end of inspiration the level of the fluid in the manometer suddenly rises several centimeters (Fig 3, B, C, D, Fig 4, D). At the end of the rise when he is asked to let out his breath there is a momentary drop in the level of fluid of about a centimeter, the pressure then rises again with continued expiration to a point dependent on conditions already described. The phenomenon was noted in six out of fifteen cases with large gas cavities, and in three out of fifteen cases with small gas cavities. It occurs with ordinary respiration as well as with forced respiration, is usually present both at the beginning and end of the seance, and it seems to be largely independent of the degree of pressure. It may be present at the initial and early operations and then disappear entirely or return some months later, also, when not present at first it may appear later (Figs 3 and 4). It is present with both types of mediastinum. When this phenomenon was first noted it was confusing, as it was feared that a reexpanded lung had been pierced, but it was invariably noted that the pressure was maintained at the end of the rise and on expiration. The importance of the phenomenon is that it makes an exception to the rule that when the needle is in the pleural space the pressure is maintained on holding the breath at the end of inspiration.

One case (Case 1) with markedly movable mediastinum (Figs 1 and 2) in which this phenomenon is present we had opportunity of examining with the fluoroscope, and a slight jerky rise of the diaphragm was noticed immediately on holding inspiration. This was seen both before and after a refill at which the beginning and ending mean pressures were -60 mm. and 0, respectively, and at which 1,400 cm. gas had been introduced. Eight roentgenograms taken of this patient's chest at different times failed to show diaphragmatic adhesions, though there was a lateral adhesion about the fourth rib. Three other cases

21 Von Adelung Jour. Am. Med. Assn., 1913, 1, 771

in which it is present, with moderately large gas cavities and each having a fairly rigid mediastinum, showed on plates some diaphragmatic adhesions as well as lateral adhesions

It is probable that this phenomenon is caused by a contraction of the lower ribs and abdominal muscles when the breath is held on inspiration, with a resulting increase of abdominal pressure and a passive rise of the relaxed diaphragm. With beginning expiration these muscles are first of all relaxed and this relaxation allows a momentary descent of the diaphragm with a resulting slight fall in intrathoracic pressure. Bittorf's<sup>18</sup> and Teske's<sup>22</sup> experiments and observations of paradoxical movements of the diaphragm are in accord with this explanation.

The practical application of these inferences may be seen from the following typical cases and accompanying charts

CASE 1—*Freely movable mediastinum* (Figs 1, 2 and 3) No 23, a woman Collapse of left lung for hemorrhage recurrent over a period of five years Left lung disseminated fibroid disease throughout, not of intense character Right lung slight infiltration above third rib

June 23, 1914 Initial reading (large-bore needle, 0.042-inch, No 19 B W G) —96 to —80 mm, deep respiration, —140 to —20, 200 cc air, ending middle pressure 0. A network of adhesions was present. The phenomenon was noted. A fairly large pneumothorax was readily obtained which ultimately required an average of 1,000 cc gas every three to four weeks. Breath sounds were almost completely suppressed after the inflation. After the fourth inflation there was no sense of pressure but the patient felt very tired for about a week after each refill. Dyspnea was felt after a mean positive pressure of 5 to 10 mm. Hyperresonance was 5 cm to the right of the mid-sternal line. The apex beat, which before the initial inflation was felt 11 cm to the left of the midsternal line, and which could usually be felt in almost the same position before a refill, became lost after one. Pulsation was occasionally seen after a refill 5 cm to the right of the midsternal line, and relative cardiac dullness noted 5 to 7 cm to the right. The characteristic curve of a movable mediastinum was early noted (Fig 3), and has been consistently maintained. The deep respirations have never been disproportionate to those of quiet breathing and their relative values have always been consistently maintained. Because of this feature and the subjective symptoms, the mean pressure was reduced to 0, or a little less. This reduction lessened the sense of fatigue somewhat and the pulse, which had averaged 90, fell to a steady rate of 80 after two weeks. The sputum, small in amount, was but little influenced. The physical signs in the right upper lobe have diminished somewhat. The general condition of the patient has materially improved and apprehension has gone. Roentgenograms (Figs 1 and 2), show a marked displacement of the heart after the refill which is materially more marked on expiration than on inspiration. There is a lateral adhesion seen about the fourth rib, but no diaphragmatic adhesion. The fluoroscope shows the greatest movement of the heart with respiration when there is a large amount of gas. The lung is not completely collapsed immediately after a refill. The yielding of the mediastinum, therefore, makes complete collapse a doubtful possibility or possible only at considerable risk. The phenomenon was present during the first five fillings and then disappeared until the ninth filling, since which time it has been usually present (Fig 3, B, C, D). Through the fluoroscope the dia-

22 Teske Munchen med Wchnschr, Sept 6, 1910, No 36, p 1892

phragmum was seen to rise in a jerky manner when the breath was held on inspiration

CASE 2—*Movable mediastinum becoming fixed* (Fig 4) No 27, a woman Right lung collapsed for severe and long standing disease Left lung slight disseminated disease throughout upper lobe

Sept 21, 1914 Initial operation, adhesions present, 200 cc gas Two days later gas was easily introduced, two sets of stationary points noted (Fig 4, A), with the mean pressures at approximately  $-20$  and  $-5$  mm, large oscillations with large-bore needle, 0.035 inch, (B W G, No 20) The further giving way of adhesions may account for these stationary points, gas 500 cc, apex beat shifts 2 cm, no material difference between the extremes of deep inspiration and expiration at the beginning and end of the operation Since the second inflation breath sounds immediately after the operation have been almost completely suppressed By December 8, seventh refill, a large pneumothorax has been obtained Hyperresonance extends 3 cm to the left of the midsternal line, the left margin of relative cardiac dullness and the apex beat have each been displaced 4 cm by the inflation Curves with stationary points have been consistently seen The rise is fairly slow, the oscillations rather irregular (B, Fig 4) January 2 The rise in pressure for a smaller amount of gas, 500 cc, is more abrupt and the oscillations are greater Two days later the patient suffered great pain at the base of the left lung, which disappeared suddenly after four days January 30, the rise in pressure is more rapid (C, Fig 4), from  $-50$  to  $+30$  mm by 450 cc gas No stationary points are noted, the oscillations are materially larger but variable, suggestion of fluid in the needle, the excursion on deep respiration has greatly increased The relative cardiac dullness is fixed at 8.5 cm to left of the midsternal line both before and after the inflation The characteristics of a fixed mediastinum are now seen, and these continue The succussion sign of fluid was obtained after the tenth refill, but was not found again At the twelfth refill the deep respiratory excursion became enormous, showing an amplitude of 230 and 220 mm before and after the inflation (D, Fig 4) The phenomenon was first seen at the end of this inflation but has since been constant It is well illustrated in the chart (Fig 4) Since the mediastinum has become fixed the pressures have been consistently raised so that now the ending mean pressure is 90 mm The patient is more comfortable, with almost entire absence of expectoration, and physically better than at any time since the pneumothorax was induced

The first case illustrates the correlation between fatigue symptoms, physical signs of displacement of the mediastinum and the data here given for inferring a movable mediastinum from the readings of the manometer Relief from the symptoms was obtained by reducing the pressure to just below zero The second case required care in the adjustment of pressure for both the functioning lung and heart Restraint was exercised in the pressure used and frequent refills were undertaken until the readily displaced mediastinum became fixed, following the pleurisy, which fixation is well shown by the manometer It then proved to be beneficial to increase the pressure and after this the intervals could be lengthened A number of other cases might be cited to show the correlation between physical signs and the manometric indications of mediastinal displacement In some cases in which the physical signs of displacement failed or were less marked, the manometer has proved a distinct help in estimating the condition of the mediastinum

## SINO-AURICULAR BLOCK DUE TO TOBACCO POISONING\*

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Sino-auricular block—standstill of the entire heart—is a rare type of arrhythmia in the adult. It is usually the result of digitalis poisoning<sup>1</sup>. Recently, however, a case due to salicylic acid has been described<sup>2</sup>. It has occasionally been induced by vagal pressure<sup>3</sup> in patients with normal rhythm and with paroxysmal tachycardia<sup>4</sup> and has frequently been induced experimentally<sup>5</sup>. The report of its occurrence as a clinical condition with accompanying graphic proof is exceedingly rare<sup>5, 6</sup>.

It has long been known that overindulgence in tobacco causes arrhythmias, but their type has not been sufficiently studied by graphic methods to determine their exact nature. I have observed several cases of extrasystoles (usually auricular), one case of auricular flutter and one of auricular fibrillation due to tobacco poisoning. As sino-auricular block has never been ascribed to this cause, the following two cases seem sufficiently noteworthy to warrant publication.

CASE 1—E. I. H., aged 28, architect, married six years, has two children. He was always athletic. When 6 years old he had diphtheria with tracheotomy, otherwise he has had no serious illness. At 15 he began smoking and has been smoking uninterruptedly since, his usual quota being three cigars and three pipefuls daily, never cigarettes. His pulse irregularity was first noticed when examined for admission to the army at the age of 20. His arrhythmia does not annoy him or in any wise interfere with his work or exercise. There was no dyspnea on exertion and the arrhythmia was not affected by exercise. There was no precordial pain or decompensation. The systolic blood pressure was 150 mm, the diastolic, 70 mm. There was a vigorous apical impulse and the cardiac sounds were normal. Orthodiascopic examination showed slight left ventricular enlargement. The urine showed no abnormalities, and examination of the abdominal organs and the nervous system revealed nothing of note. The heart contracted regularly at the rate of about 100 per minute for two, three, or four beats and then there was a sudden pause during which no sound was heard at the apex nor any pulse beat felt at the wrist. Examination of the

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1 Hewlett Jour Am Med Assn, 1907, lvii, 47. Rühl Deutsch Arch f klin Med, 1908, xciv, 286. Cohn and Fraser Seventeenth International Congress of Medicine, 1913, Section 6, Medicine.

2 Sicard and Meara Am Jour Med Sc, 1915, cl, 843.

3 Robinson and Draper Jour Exper Med, 1911, xiv, 217. Von Hoesselin Deutsch Arch f klin Med, 1914, cxiii, 537.

4 Cohn and Fraser Heart, 1913-14, v, 93.

5 Eyster and Evans THE ARCHIVES INT MED, 1915, xvi, 832.

6 Lewis Clinical Electrocardiography, p 100.



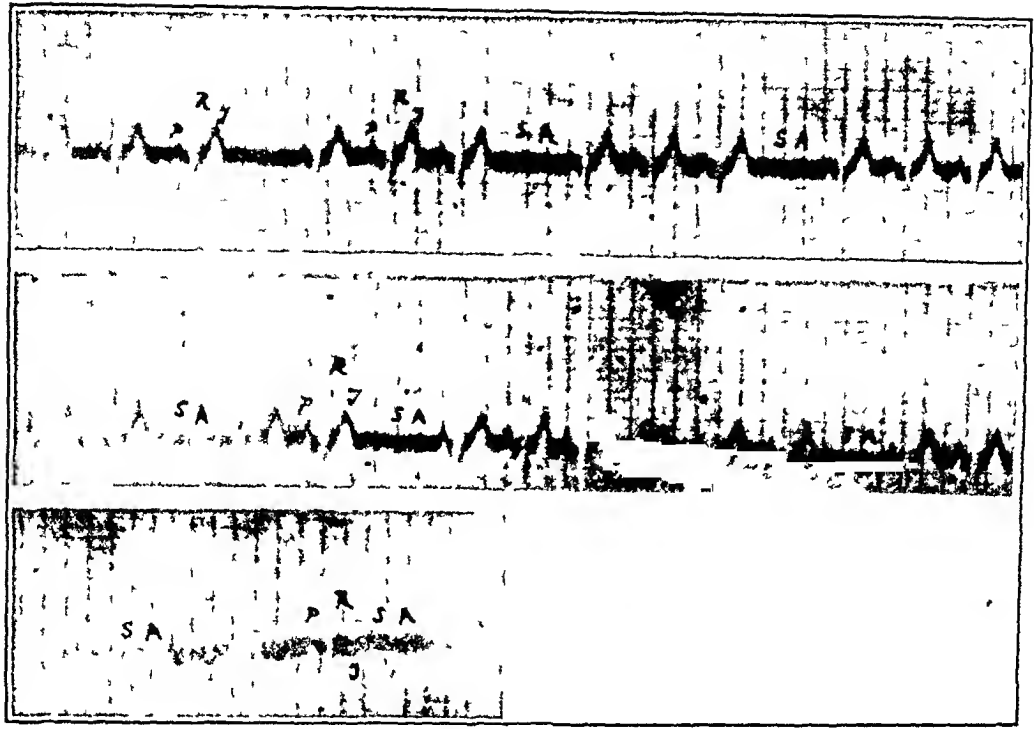


Figure 1

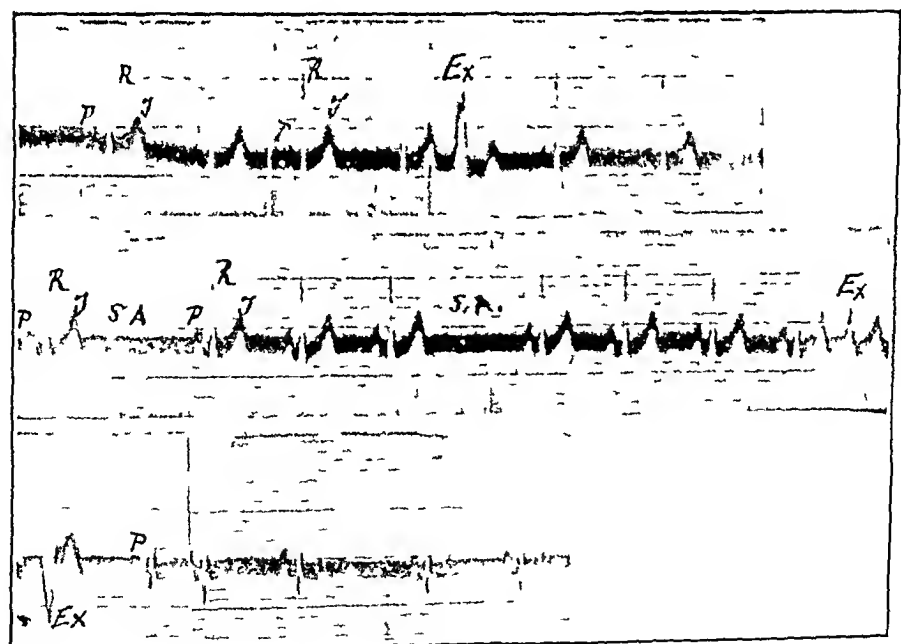


Figure 2

Figure 1—Electrocardiogram from Case 1 In this figure and Figure 2 the vertical lines measure one-fifth second, the different leads are marked 1, 2, 3, P=the auricular, R-T, the ventricular complex SA=sino-auricular block, Ex=ventricular extrasystole

electrocardiogram (Fig 1) showed sino-auricular block, a sudden arrest of the whole heart (S A, Fig 1) The length of most of the pauses was somewhat less than two normal beats, a condition ordinarily found in this type of arrhythmia The patient refused to stop smoking, the arrhythmia continued This case was uncomplicated by any evidence of organic cardiovascular disease

CASE 2—A B, physician, aged 57, always led a very active life, had been a heavy and constant cigaret smoker since youth, averaging thirty cigarettes daily Several years ago he was treated medically for duodenal ulcer and has had no symptoms since During the last eight years he has complained of some dyspnea In addition, for the last two or three years he has had occasional attacks of precordial pain For several months both symptoms have become worse His pulse irregularity began eight months ago The patient was somewhat stout, his color pasty gray The average systolic blood pressure was 150 mm, the diastolic, 100 mm There was no pain on precordial pressure Except for a faint systolic murmur at the right base, the heart sounds were normal The orthodiascope showed that the aortic arch and left ventricle were somewhat enlarged The neurological status was normal There was slight edema of the legs On one examination the urine contained a few hyaline casts and a slight trace of albumin Extrasystoles were heard at the apex and transmitted to the wrist about once in every three or four beats, their number decreased after exercise Besides the extrasystoles, there were occasional complete pauses of the heart and pulse, the electrocardiogram (Fig 2, lead 2, S A) showed that the pauses were due to sino-auricular block and almost equalled two normal contractions Ventricular extrasystoles (Fig 2) were seen in the different leads The ventricular rate, when rhythmical, was about 80 per minute, the conduction time (P-R interval), normal The patient was advised to stop smoking and moderate doses of bromids were prescribed The sino-auricular block disappeared within three days and has not since returned The extrasystoles also disappeared for a few days, but then recurred about once every minute, after two weeks they were as frequent as at the first examination With their return, precordial pains and dyspnea increased Digipuratum tablets, three daily, and theobromin sodium salicylate, with Karrel diet, once weekly, were prescribed, and the patient's work was somewhat restricted Within three weeks, the extrasystoles, precordial distress and dyspnea entirely disappeared Except for occasional ventricular extrasystoles following extreme effort, the patient feels quite comfortable

A study of the history and clinical course showed that the two distinct types of arrhythmia, sino-auricular block and ventricular extrasystoles, were apparently caused by two different factors, the former by tobacco, the latter probably by myocarditis and nephritis The sino-auricular block disappeared very soon after smoking was stopped, the extrasystoles, only when compensation was fully restored Ventricular extrasystoles are known to accompany any type of cardiovascular disease with decompensation With restoration of compensation they usually disappear, a result that was accomplished in this case

#### COMMENT

Sino-auricular block is commonly ascribed to a vagus influence acting on the sinus region of the heart in which lies the pacemaker (the sino-auricular node) with its rich nerve plexuses and ganglia, morbid vagus influences may block out an entire sequential auriculo-

ventricular contraction and produce a corresponding pause of cardiac activity. In animals the experimental effects on the heart and aorta of nicotin injections and of tobacco inhalations and their possible correlation with similar cardiovascular disease in man are still disputed questions and have no bearing on the subject matter of this paper. These observations, however, have tended to minimize the definitely known poisonous effects of nicotin on nerves and nerve endings. Langley and Sherrington<sup>7</sup> were among the first to demonstrate the neurotropic effects of nicotin, the most active of the tobacco alkaloids. Pezzi and Clerc<sup>8</sup> studied the effects of nicotin injections upon cardiac rhythm and divided these into an initial bradycardial, and a later tachycardial, phase. In the former, they occasionally noted auricular arrest with ventricular arrhythmia, and less frequently auricular fibrillation, with the tachycardia, they observed lessened auriculoventricular conduction time, retrograde conduction, auricular extrasystoles or incomplete auriculoventricular dissociation. Cushny<sup>9</sup> showed that experimental nicotin injections disturbed normal cardiac rhythm mainly by a morbid neurotropic influence acting on the ganglionic terminations of the vagus and sympathetic nerves, thus it seemed possible to have two opposite effects on heart rate—abnormal slowing or acceleration—apparently depending on the preponderant selective action for vagus or accelerator nerve endings. That such action may rapidly shift from one to the other seems plausible from our present scanty clinical knowledge that nerve tone may be a very unstable quality, at times readily influenced.

The clinical cases here reported seem to substantiate, in a degree, the results of animal experimentation. In Case 2, the extrasystoles were the result of decompensation. The sino-auricular block represented the effects of nicotin poisoning on the vagus alone. Patient 1 had no organic disease. The moderate acceleration interspersed with irregularly occurring sino-auricular block was apparently a clinical prototype of the two opposed experimental effects of the tobacco alkaloid on the vagus and accelerator.

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7 Langley and Sherrington *Jour Physiol*, 1891, *xii*, 43

8 Pezzi and Clerc *Jour de physiol et path gen*, 1913, *xv*, 1

9 Cushny *Pharmacology and Therapeutics of the Action of Drugs*, 1913, p 272

# OBSERVATIONS ON THE TYPHOIDIN REACTION\*

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AND

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In every community in which typhoid fever is endemic, the desire exists for a method of determining the presence or absence of immunity to the disease

A test that could be relied on to furnish an index of resistance to invasion by the typhoid bacillus, would determine the need of prophylactic vaccination or revaccination, and in certain less common instances, perhaps afford the means of identifying a previous obscure infection as typhoid fever. The shortcomings of the ordinary immunological procedures for this purpose, long recognized, were emphasized anew by Gay and his co-workers, who devised the typhoidin reaction to supplement them.

Gay and Force<sup>1</sup> prepared an extract of the typhoid bacillus according to the technic employed by Koch in the preparation of "Original Tuberculin," 250 c c of 5 per cent glycerin broth were inoculated with a strain of *Bacillus typhosus* (Dorset Army Strain No 5), and incubated for five days. The culture was then reduced without filtration to one-tenth of its original volume by evaporation over an acetone bath at 56 C for about eight hours. The end product they named "typhoidin."

For control tests, 5 per cent glycerin broth was concentrated at the same time and by the same means to an equivalent volume.

The method of carrying out the original tests was essentially that utilized by von Pirquet in eliciting the cutaneous tuberculin reaction. It consisted in producing an abrasion of the skin, of uniform size and depth, designed to cut just through the epidermis of the arm without drawing blood. The abrasion was produced by making a twist of a chisel with a straight edge, 2.25 mm wide, with square corners, and tempered to resist sterilization by burning alcohol. The skin was cleansed with 95 per cent alcohol. Two uniform abrasions were made on the upper arm or forearm, and with a sterile toothpick the control solution was rubbed into the inner spot and the typhoidin solution was applied to the outer one. The reactions were observed six and twenty-

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\* From the Medical Clinic of the Johns Hopkins Hospital

1 Gay, F P, and Force, J N. THE ARCHIVES INT MED, 1914, LIII, 471

four hours later, and rarely at subsequent periods. In a few instances an accelerated response was noted after six hours, but this subsided within twenty-four hours. Not infrequently a positive reaction persisted for a week. Generally, the control spot showed a healed abrasion 2 mm in diameter, not surrounded by an areola. In fewer instances, a slight zone of traumatic redness was seen about the abrasion. In the latter group, when there was a positive reaction about the typhoidin spot, the difference between its areola and the redness about the control spot was readily measured. As evidence of a positive reaction, a difference of 2.5 mm between the two areolas was arbitrarily chosen. The positive spot measured from 4 to 12 mm in diameter, was usually somewhat indurated and often clearly demarcated. In negative cases the same response was noted in the control and in the typhoidin spot.

The results of the application of this test by Gay and Force may be briefly summarized.

Of 21 cases with a definite history of typhoid fever from four and a half months to four years previously, 20 gave a positive reaction.

Of 6 cases with a history suggesting typhoid fever in the past, 6 gave a positive test.

Of 41 negative control cases, 35 gave negative tests and the remaining 6 "may be suspected of having had a mild and undiagnosed attack of typhoid fever."

Of 15 individuals vaccinated with Army vaccine, eight months to four and three-fourths years previously, 9 reacted positively.

Twenty-five individuals vaccinated with the sensitized vaccine of Gay and Claypole one to eight months before the test, all developed a positive reaction.

In a later communication, Gay and Claypole<sup>2</sup> reported the results of the typhoidin test made with a modified test preparation injected intradermically.

Original typhoidin solution was precipitated with twenty volumes of alcohol, filtered, and the filtrate, after being washed with absolute alcohol and ether, was dried on porcelain plates in a vacuum over sulphuric acid. The control 50 per cent glycerin broth was similarly treated. For the tests a small amount of each sediment was dissolved in phenolated saline solution equivalent to the original volume of concentrated typhoidin or even to a double concentrated solution. Such solutions when kept in a cool place gave a reaction in typhoid immunes for at least a month.

The exact amount of typhoidin used in carrying out the intradermic test is not mentioned. The only statement as to the quantity of the

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2 Gay, F. P., and Claypole, E. J. *THE ARCHIVES INT. MED.*, 1914, *xiv*, 671.

preparation employed is that "the tests were applied by making blebs, one on each upper arm"

The results of the typhoidin skin test summarized in this communication indicated that 95 per cent (40 of 42) individuals with a history of having had typhoid fever gave positive reactions, and that of control persons with no history of the disease 86 per cent (38 of 44) gave negative reactions. Further, of 6 persons reacting positively, 5 probably had had abortive typhoid fever.

Gay and Claypole found that individuals immunized with typhoid vaccine "reacted in the majority of cases for about two years and then became more frequently negative," and inclined to the view that "a negative skin test at least a month after vaccination indicated the need of revaccination."

The evidence that a positive skin test with typhoidin indicated immunity to typhoid fever was further supported by similar reactions induced in immunized rabbits.

The studies of Gay and Force and of Gay and Claypole seemed to show that a satisfactory gage of resistance to infection with the typhoid bacillus had been found.

Nichols<sup>3</sup> carried out both the dermal and the intradermal tests of Gay. The former reaction yielded disappointing results, due, he thought, to the deterioration of the typhoidin solution. The reactions made with the precipitated preparation gave positive results in 75 per cent of persons who had had typhoid fever, and in 64 per cent of fifty persons who had never had typhoid fever but who had received prophylactic vaccine within four years.

Pulay<sup>4</sup> published the results of a series of tests carried out on one hundred thirteen persons, some of whom had had typhoid fever recently or some time before, some of whom had received antityphoid vaccine, and others of whom gave a negative history. Apparently, his findings confirm those of Gay and Force and of Gay and Claypole.

The need for such a test in the medical department of the Johns Hopkins University and Hospital has long been recognized. The large student body, the corps of nurses, the staff, the majority of whom receive prophylactic vaccination against typhoid fever, constitute a group the resistance of which to infection with the *Bacillus typhosus* it is expedient to know. Accordingly, the following observations were made.

In order to make the results of these observations as nearly comparable as possible, the typhoidin was prepared strictly according to

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3 Nichols, H. J. Jour. Exper. Med., 1915, xxii, 780.

4 Pulay, E. Wien klin. Wchnschr., 1915, xxviii. The original article was not to be obtained. The quoted data were contained in an abstract in Jour. Am. Med. Assn., 1916, lxi, 230.

the technic of Gay, and, for the sake of emphasis, it is again detailed. Two hundred fifty cubic centimeters of 5 per cent glycerin broth were inoculated with *Bacillus typhosus* (Army Strain "Rawlings") and incubated for five days at 37 C. The culture was then evaporated at 56 C without filtration to one-tenth of its original volume, and precipitated with ten volumes of absolute alcohol. The precipitate, washed with absolute alcohol and ether, was then desiccated in a vacuum over calcium chlorid.

The control preparation was prepared by treating uninoculated sterile 5 per cent glycerin broth in the same way. The end product in each instance was a slightly tinted white cake which, when ground in a mortar, yielded a fine white powder readily soluble in water or in salt solution.

No cutaneous tests were made. In each case a known weighed quantity of the typhoidin, dissolved in a constant volume of 0.85 per cent salt solution, was injected into the skin of the upper arm or forearm after it had been cleaned with alcohol. At the time of the injection of the typhoidin solution, an injection of an equal amount of the control solution was given. The results of the inoculations were noted immediately, after six hours, twenty-four hours, and often at daily intervals for a week.

In the major part of the series to be recorded, a polyvalent typhoidin was used. This was prepared according to the described technic, but the end product represented the combined precipitates of cultures of thirty-five strains of the typhoid bacillus.

In carrying out the tests from 0.00001 to 0.02 gm. of typhoidin was used. The solution of typhoidin was made in 0.85 per cent salt solution and was injected within two hours of its preparation.

Within a few minutes to half an hour after the injection, an erythema 0.5 to 2.0 cm. in diameter developed, in the center of which there was usually a small area of edema. During the next few hours the erythema continued to spread and the central edema subsided, leaving at the site of the injection a slightly elevated indurated nodule, the skin over which was darker than the surrounding area.

When small doses, such as 0.00005 gm. or less, of typhoidin were used, the reaction was purely local and reached its maximum within twenty-four hours, when there was generally a small, broad nodule at the site of the puncture. This was surrounded by a zone of erythema that varied in size but was rarely greater than 5 or 6 cm. in diameter. The color faded during the next twenty-four hours, leaving a small central stain that at times persisted several days or even a week.

When larger amounts of typhoidin were injected, the resultant reaction was similar but of greater extent. In addition, any or all

of the following signs occasionally developed. Marked local tenderness, heat and swelling, pain when the elbow was flexed, lymphangitis, axillary lymphadenitis, even slight fever and malaise.

Occasionally the erythema was sharply demarcated, but more often it was diffuse and its outlines so difficult to discern that accurate measurements of its extent could not be made. This was especially true of the superior margin, for the erythema often extended up the arm in a gradually fading band.

A reaction following the intradermic injection of solutions containing less than 0.0001 gm of the precipitate from the uninoculated broth was usually lacking. In those instances in which larger amounts were used, a small zone of slight erythema resulted.

#### RESULTS OF THE TESTS

##### A. INDIVIDUALS WITH A RELIABLE HISTORY OF TYPHOID FEVER

The test was carried out in ten individuals who had had typhoid fever. The time that had elapsed since the infection, the amount of typhoidin injected, and the reaction elicited, are summarized in Table 1.

TABLE 1—TYPHOIDIN TEST OF INDIVIDUALS WHO HAD HAD TYPHOID FEVER

Name	History	Typhoidin, Mg	Reaction 24 Hours		Name	History	Typhoidin, Mg	Reaction 24 Hours	
			Test Cm	Control Cm				Test Cm	Control Cm
I	Typhoid fever 10 yrs ago	1/4	6 × 10		H	No typhoid or vaccine	1/4	7 × 11	
F	Typhoid fever 1° normal 1 mo	1/4	10 × 15		P	No typhoid or vaccine	1/4	6 × 10	
S	Typhoid fever 1° normal 1 mo	1/10	4 × 8	1 × 1	M	No typhoid or vaccine	1/10	5 × 5	1 × 1
W	Typhoid fever 1° normal 1 mo	1/10	4 × 8	N P	H	No typhoid or vaccine	1/10	3 × 6	N P
F	Typhoid fever 1° normal 1 mo	1/10	4 × 6	N P					
M	Typhoid fever 10 yrs ago	1/20	4 × 5	0.5 × 0.5	H	No typhoid or vaccine	1/20	5.5 × 10	0.5 × 0.5
P	Typhoid fever 8 yrs ago	1/20	6 × 8	0.5 × 0.5	N	No typhoid or vaccine	1/20	3.5 × 6	N P
H	Typhoid fever 12 yrs ago	1/20	3 × 2.5	N P	A	No typhoid or vaccine	1/20	3 × 4.5	N P
R	Typhoid fever 15 yrs ago	1/40	5.5 × 11	N P	H	No typhoid or vaccine	1/40	4 × 9	N P
					C	No typhoid or vaccine	1/40	3.5 × 4	N P
B	Typhoid fever 6 mos ago	1/100	2 × 2.5	N P	J	No typhoid or vaccine	1/100	3 × 4.5	N P

N P = needle puncture

Accepting as the criterion of a positive reaction a difference of 2.5 mm in diameter between the areola resulting about the site of the injection of the typhoidin and that developing around the injection site of the control preparation, all ten of these individuals gave a positive reaction, but an identical procedure carried out in ten persons who had never had typhoid fever any illness that was probably abortive typhoid fever, or a prophylactic typhoid vaccination showed a similar result.



TABLE 2—TYPHOIDIN TESTS OF INDIVIDUALS WHO HAD RECEIVED PROPHYLACTIC ANTITYPHOID VACCINATION AND OF THOSE WHO HAD NOT HAD ANTITYPHOID VACCINATION OR TYPHOID FEVER

Name	History	Typhoidin, Mg	Reaction 24 Hours		Name	History	Typhoidin, Mg	Reaction 24 Hours	
			Test Cm	Control Cm				Test Cm	Control Cm
G	Vaccine 1½ yrs ago	1/4	6 × 10		A	No typhoid fever or vaccine	1/4	6 × 12	
M	Vaccine 4 mos ago	1/4	7 × 11		H	No typhoid fever or vaccine	1/4	5 × 12	
B	Vaccine 6 mos ago and 3 yrs ago	1/4	6 × 8						
S	Vaccine 1½ yrs ago	1/10	5 × 10	0.5 × 0.5	T	No typhoid fever or vaccine	1/10	5 × 10	2 × 1
J	Vaccine 1 yr ago and 3 yrs ago	1/10	5 × 10	0.5 × 0.5	C	No typhoid fever or vaccine	1/10	4 × 6	N P
M	Vaccine 3 mos ago	1/10	5 × 9	N P*	R	No typhoid fever or vaccine	1/10	6 × 11	N P
H	Vaccine 3 mos ago and 3 yrs ago	1/10	3.5 × 4	N P					
K	Vaccine 8 mos ago	1/10	5 × 10	0.5 × 0.5					
W	Vaccine 3 yrs ago	1/20	3 × 6	1 × 1	A	No typhoid fever or vaccine	1/20	3 × 4.5	N P
A	Vaccine 2 yrs ago	1/20	3 × 5	0.5 × 0.5	H	No typhoid fever or vaccine	1/20	5.5 × 10	0.5 × 0.5
M	Vaccine 2 yrs ago	1/20	2 × 4	0.5 × 0.5	M	No typhoid fever or vaccine	1/20	4.5 × 6	N P
S	Vaccine 2 yrs ago	1/20	3 × 2.5	0.5 × 0.5					
L	Vaccine ½ yr ago	1/20	2 × 2	N P					
B	Vaccine three courses in past 1 yr	1/20	4 × 6	0.5 × 0.5					
M	Vaccine 2½ yrs ago	1/20	4.5 × 9	N P	L	No typhoid fever or vaccine	1/20	3 × 5	N P
S	Vaccine 1½ yrs ago and 3½ yrs ago	1/20	4.5 × 9	N P	J	No typhoid fever or vaccine	1/20	3 × 6	N P
T	Vaccine 2 yrs ago	1/20	5 × 10	N P	P	No typhoid fever or vaccine	1/20	5 × 7	N P
T	Vaccine 2½ yrs ago	1/20	3.5 × 6	N P					
C	Vaccine 1½ yrs ago and 3 yrs ago	1/20	5 × 6.5	N P					
H	Vaccine 1 yr ago and 3½ yrs ago	1/20	3.5 × 6	N P					
H	Vaccine 2 yrs ago and 4 yrs ago	1/40	4 × 7	N P	W	No typhoid fever or vaccine	1/40	2 × 4.5	N P
W	Vaccine 3½ yrs ago	1/40	3.5 × 5	N P	T	No typhoid fever or vaccine	1/40	2.5 × 6.5	N P
P	Vaccine 6 mos ago	1/40	3 × 4	N P	P	No typhoid fever or vaccine	1/40	2 × 1.5	N P
D	Vaccine 3 yrs ago	1/40	2 × 7	N P					
R	Vaccine 18 mos ago and 3 yrs ago	1/40	3 × 3	N P					
M	Vaccine 6 mos ago	1/40	4 × 5	N P					
S	Vaccine 4 mos ago and 4 yrs ago	1/100	2 × 4	N P	G	No typhoid fever or vaccine	1/100	3 × 4.5	N P
O	Vaccine 8 mos ago and 2 yrs ago	1/100	1.5 × 2	N P	B	No typhoid fever or vaccine	1/100	1.5 × 3	N P
					K	No typhoid fever or vaccine	1/100	3 × 4	N P
					B	No typhoid fever or vaccine	1/100	1.8 × 2.5	N P

N P = needle puncture

## B INDIVIDUALS WHO HAD RECEIVED PROPHYLACTIC ANTITYPHOID VACCINATION

Twenty-eight medical students and physicians, who had received one or more courses of injections of typhoid vaccine three months to five years ago, were each given an intradermic injection of typhoidin solution. The dosage used and the extent of the reaction that followed are seen in Table 2.

These results again show in all cases the chosen criterion of a positive reaction. But as in Series A, so in this series, a comparison of these tests with those obtained in normal controls who had never had typhoid fever, any illness that suggested typhoid fever or antityphoid vaccination, shows identical findings.

C INDIVIDUALS WHO HAD NOT HAD TYPHOID FEVER OR  
PROPHYLACTIC ANTITYPHOID VACCINATION

The test was carried out in twenty-five such people, and the results have been recorded in Tables 1 and 2. These findings need little comment. It is not likely that more than a small percentage of these individuals could have had an unrecognized attack of typhoid fever, and even more improbable that any large proportion of them possessed a natural immunity to the disease.

## CONCLUSION

The typhoidin reaction carried out in sixty-six individuals failed to furnish data by means of which it was possible to differentiate between those who had neither had typhoid fever nor received prophylactic vaccination and those who had either had the disease or had been artificially immunized against it.

# STUDIES OF THE HEART'S FUNCTIONAL CAPACITY AS ESTIMATED BY THE CIRCULATORY REACTION TO GRADUATED WORK<sup>1</sup>

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The method used in these studies to determine the heart's functional capacity consisted briefly in the deductions made from frequent measurements of the pulse and systolic blood pressure after increasing amounts of work as described in a former article<sup>1</sup>. When the highest blood pressure was noted immediately after work and then quickly subsided this work was considered to have been within the heart's capacity. When, on the other hand, the highest pressure was reached a minute or two after the completion of work, at a time when the pulse had dropped back towards normal, that work was regarded as having overtaxed the heart.

Graduated work was furnished in a few experiments by a bicycle ergometer of the type described by Krogh and Lindhard,<sup>2</sup> but in the majority of cases by movements of flexion, extension and swinging with iron dumb-bells weighing from 3 to 20 pounds each.

Dumb-bells afford a most practical means of furnishing graduated work either for testing the heart's functional capacity or for the treatment of patients convalescing from cardiac insufficiency. Computation of the amount of work performed through dumb-bell exercises is, however, not absolute, as will be seen from the following examples. If a 5-pound dumb-bell is extended upward from the shoulder through 2 feet, 10 foot-pounds of work is performed with each extension. With a 10-pound bell 20 foot-pounds, or twice as much work, would be performed in the same space of time. Yet these figures do not represent the entire amount done, as two sources of work have been ignored.

During the time consumed in the exercise the bell is being supported near the shoulder, which entails muscular effort. Also when the bell returns to the shoulder some force is exerted to prevent too rapid a fall. Considerable additional work which cannot be estimated in foot-pounds is performed in these ways. The actual work done

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\* From the Medical Service of the House of Relief

1 Barringer, T. B., Jr. *THE ARCHIVES INT. MED.* 1916, LVII, 363

2 Krogh and Lindhard. *Skandinavisches Arch. f. Physiol.* 1913, LXX, 378

by the extension or flexion of dumb-bells is therefore the sum of three parts. The first, which arises from moving the bell through a certain distance, we can measure, the second, arising from supporting the bell, and the third, derived from muscular resistance, we cannot measure. Although this limitation makes our estimations relative and not absolute, it does not invalidate comparisons of the heart's efficiency obtained by means of this measurable component of dumb-bell work. An idea of the number of foot-pounds which elude computation in this way may be gained by a consideration of the heart's capacity as calculated absolutely through work on the bicycle ergometer.

A laboratory assistant, aged 23 years, with a normal heart, and in fair physical training, was able to do 8,700 foot-pounds per minute for five minutes on the bicycle ergometer without overtaxing his heart. Working at the rate of 8,900 foot-pounds per minute, however, in two minutes he had overtaxed his heart. Another assistant, aged 21 years, with a normal heart, but with not quite as powerful a physique as the first man, was able to do 7,200 foot-pounds per minute for four minutes on the ergometer. At the rate of 9,900 foot-pounds per minute his heart's capacity was exceeded in two and a half minutes. For comparison the cardiac efficiencies of two young men, a few years older, with normal hearts and in fair training, were determined by graduated work with dumb-bells. One was able to do 9,600 foot-pounds in sixty seconds, but working at the same rate for ninety seconds his heart was overtaxed. The other man did 7,600 foot-pounds in sixty seconds, but was unable to continue at this rate for ninety seconds without exceeding his heart's capacity.

Again, a patient convalescing from cardiac insufficiency was able to do 1,300 foot-pounds per minute on the ergometer for two and a half minutes with normal circulatory reaction. The same day 1,200 foot-pounds of dumb-bell work in sixty seconds overtaxed his heart.

The disparity thus shown between the values obtained in these experiments with the ergometer and those obtained from dumb-bell exercise is large and must represent that part of dumb-bell work which we cannot translate into work units.

In the light of the preceding explanation it is clear, we trust, that the values stated in the subsequent studies of the heart's efficiency as determined by graduated dumb-bell work are all considerably lower than they should be and yet they afford a fairly accurate means of comparison.

Table 1 represents the functional capacities of the hearts of normal persons as determined by graduated dumb-bell work and by the ergometer.

TABLE 1 — FUNCTIONAL CAPACITY OF NORMAL HEARTS AS ESTIMATED BY GRADUATED WORK WITH DUMB-BELLS AND WITH THE BICYCLE ERGOMETER

## DUMB-BELL WORK

Case	Name	Age	Sex	Number of Foot Pounds for Which Heart Can Supply Blood to Muscles	No. of Foot Pounds by Which Heart is Overtaxed to Supply Blood to Muse
1	B	56	♀	1700 in 30 sec	2000 in 30 sec
2	R	39	♀	2200 in 60 sec	2600 in 30 sec
3	D H	23	♀	4500 in 60 sec	4600 in 60 sec
4	H	45	♂	2600 in 45 sec	3000 in 45 sec
5	T H	40	♂	8200 in 60 sec	11000 in 60 sec
6	B	37	♂	7000 in 60 sec	8500 in 60 sec
7	L	44	♂	6500 in 60 sec	7800 in 60 sec
8	V	26	♂	9600 in 60 sec	10600 in 60 sec

## ERGOMETER

9	S	23	♂	43500 in 5 min	17800 in 2 min
10	M	21	♂	28800 in 4 min	24500 in 2½ min

A comparison between Cases 1 and 3 is interesting. Patient 1 was a woman, aged 56, who had never taken any more vigorous exercise than an occasional walk. Patient 3 was a woman 23 years old, in excellent physical condition, who played tennis and swam occasionally.

Patient 4 was a professional man, aged 45, who had taken practically no vigorous physical exercise since boyhood, because when he did so he became short of breath and felt exhausted afterwards. His heart was apparently normal in every respect, but his cardiac capacity was the lowest of twenty normal men of middle age. By a course of graduated exercise his heart's efficiency was increased so that he could do 6,400 foot-pounds in sixty seconds, instead of 2,600 foot-pounds in forty-five seconds which was his initial capacity.

Three cases have been selected to illustrate the course of the heart's functional capacity in patients suffering from varying degrees of decompensation. The first patient, J. C., a watchman, 54 years old, had had his first attack of cardiac insufficiency in 1913, having at that time swelling of the feet and legs, and shortness of breath. On Sept. 8, 1915, he was admitted to the House of Relief complaining of the same symptoms. He was a thin man with gray hair, dyspneic, and with markedly swollen legs and scrotum. The heart was enlarged and showed an aortic and mitral regurgitation. There were signs of small quantities of fluid in both pleural cavities. The liver was decidedly enlarged, and the blood showed a +++ Wassermann reaction. He

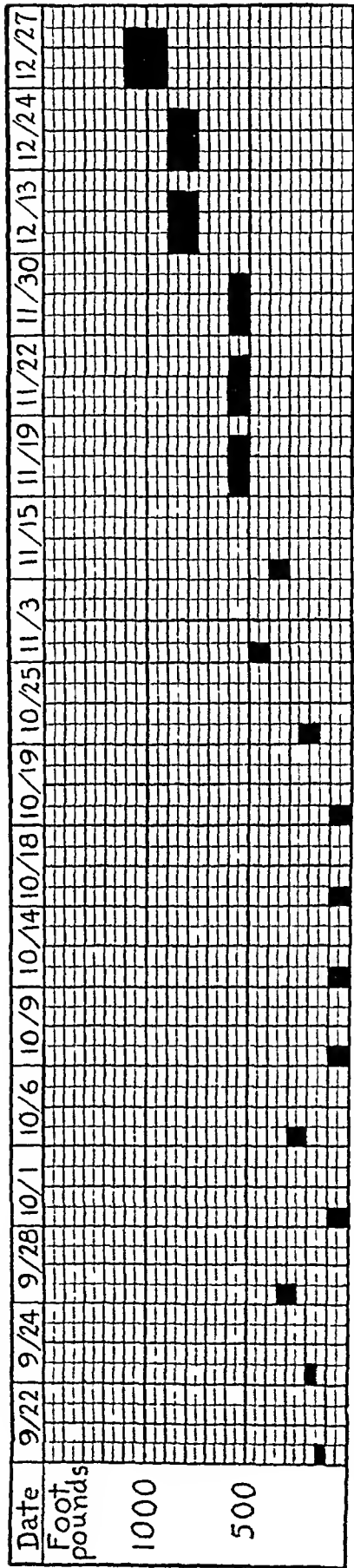


Chart 1.—Course of the heart's capacity in J. C., suffering from aortic regurgitation and cardiac insufficiency. In this and the following charts each space between two consecutive perpendicular lines represents 15 seconds. The black squares represent the heart's capacity. For illustration, on September 22, the heart, without being overtaxed, was able to supply sufficient blood to the muscles to enable them to do 100 foot-pounds in 15 seconds. The performance of 150 foot-pounds in 15 seconds overtaxed the heart. So the capacity is represented by the black square lying between 100 and 150 foot-pounds.

received altogether 16 drams of tincture of digitalis and twenty intra-muscular injections of salicylate of mercury. September 22, the cardiac capacity was tested and the patient was given a course of graduated exercise. A few days after the exercise began the digitalis was stopped. Chart 1 represents the course of the heart's functional capacity.

September 22, when he was able to walk slowly around the ward for a short distance, his cardiac capacity was very low. On December 27, when his capacity had increased to between 900 and 1,100 foot-pounds performed in 60 seconds, he was much stronger and able to do light work.

The second patient, C. G., was a salesman, aged 31 years, who had had four attacks of acute rheumatic fever. For two years he had had occasionally symptoms of cardiac insufficiency, but for 6 months past decompensation had been marked. On June 8, 1915, physical

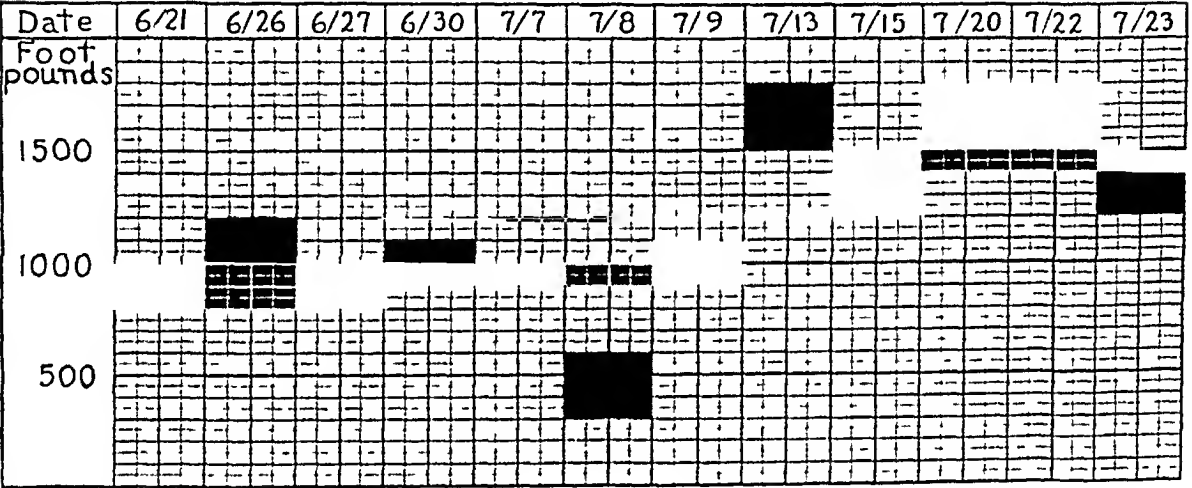


Chart 2—Course of the heart's capacity in patient C. G., suffering from mitral regurgitation and cardiac insufficiency.

examination showed a pallid man, weighing 192 pounds, dyspneic, and with swollen legs. The heart was decidedly enlarged, regular and rapid in action, and showed a mitral regurgitation. The edge of the liver was felt 6 inches below the free border of the ribs in the mid-clavicular line. There was also a small amount of fluid in the right pleural cavity. The patient was given 6 drams of tincture of digitalis, and June 21 a course of graduated exercise with dumb-bells and bars was begun. Chart 2 shows the course of the heart's capacity.

On June 21, when the cardiac capacity was 800 foot-pounds in sixty seconds he was able to come to the office daily for treatment, walking two blocks each time. On July 23 he was able to do between 1,200 and 1,500 foot-pounds in sixty seconds and he felt strong enough to go to his own office three times weekly.

The third patient, F W, was a woman aged 27 years, who for some years had had a mitral regurgitation, with slight enlargement of the heart, but no symptoms of cardiac insufficiency except slight palpitation on exertion. The origin of the heart's condition was unknown. The patient had been careful to avoid physical exertion for several years. She was given a course of graduated exercises.

Chart 3 represents the course of the heart's capacity.

Our experience in estimating the heart's functional capacity by means of dumb-bell movements in a large number of persons suffering

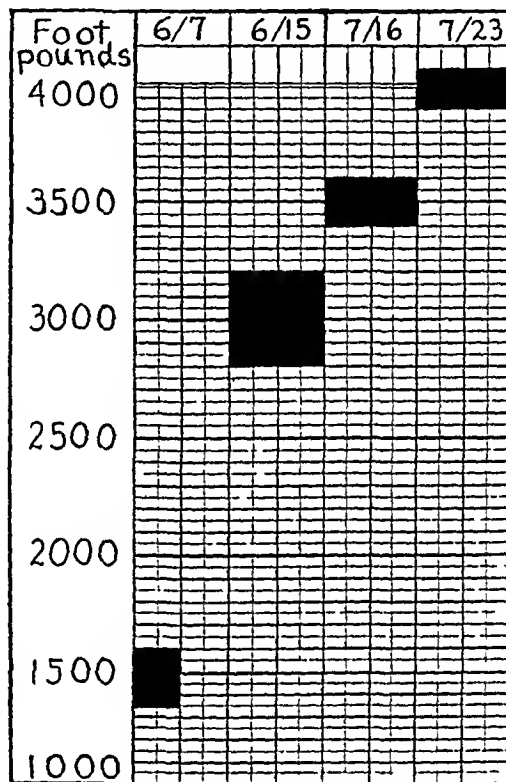


Chart 3—Course of the heart's capacity in F W, suffering from well-compensated mitral regurgitation

from cardiac insufficiency leads us to make the following statements with considerable confidence.

Patients with cardiac capacities under 100 foot-pounds per minute, generally show other signs of cardiac insufficiency. In old people, however, the heart's capacity may be very low and yet no physical sign of cardiac insufficiency be present.

Patients with capacities between 100 and 1,000 foot-pounds per minute are progressively able to be up and about and to do some walking.

A cardiac capacity under 1,000 foot-pounds per minute affords important confirmatory evidence of the existence of suspected myocardial disease.



Although the values of the heart's capacity as estimated in these studies are not absolute, the conception they give us of the heart's function does much to establish a new viewpoint in circulatory physiology

I am much indebted to Dr A C Sinton and Dr I B Ridgeway, house physicians at the House of Relief, for their help in carrying out the work outlined above

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# THE PRESENT STATUS OF MAGNESIUM SULPHATE IN THE TREATMENT OF TETANUS \*

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Ever since the introduction of antitetanus serum by Behring and Kitasato<sup>1</sup> in 1890 there has been more or less increasing disappointment because of the numerous failures after the therapeutic application of this agent. Indeed it was early recognized, even by those who claimed great merit for antitoxin, that in most cases of tetanus it was absolutely necessary to employ other means for the control of violent spasms and the conservation of the patient's strength. Even if, in the end, the serum could neutralize and render harmless the otherwise fatal toxin, it had no immediate effect upon the exhausting and dreaded muscular paroxysms.

Consequently, for the relief of these conditions the attending physician was forced to utilize those sedative and anesthetic drugs, which, in one form or another, have been employed in tetanus ever since the disease has been known. In this, as in other diseases, there would occasionally appear writers whose enthusiastic support for one or the other remedy would, for a time, engender the hope that some really life-saving treatment had been devised, only later to be succeeded by discouragement and therapeutic nihilism as the apparent futility of any remedy whatsoever appeared to have become firmly established. The difficulties in the way of finding the ideal drug were almost insuperable.

The advantages in the use of antitoxins consist chiefly in the fact that their therapeutic effect is obtained without costing the patient one iota of his strength or bodily resistance. In short, for the patient's body, if not for his pocketbook, these remedies are the cheapest known. On the other hand, most antispasmodic and anesthetic agents, such as chloral, opium, chloroform, etc., achieve results by a toxic action and, consequently, for whatever measure of relief the patient obtains, he must pay the price. The more relief he demands, the greater this price becomes until finally the choice must be made as to whether it would be better to die from the toxic action of the disease or from the toxic action of its treatment.

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<sup>1</sup> Behring and Kitasato. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Tieren, Deutsch med Wchnschr, 1890 No 49, p 1113

Naturally then, when a new drug was proposed or sponsored, it became necessary to examine its merits closely, not only as to its specific therapeutic possibilities, but also as to its comparative freedom from toxic effects. A decision on these points has not always proved to be an easy one and no remedy of modern times has furnished a better example of this fact than has magnesium sulphate<sup>2</sup> in relation to the treatment of tetanus.

When the use of this salt was first proposed it was welcomed with enthusiasm because it apparently possessed many of the required characteristics of an ideal antispasmodic and anesthetic drug. The early belief was in a measure supported by experiments on animals and the successful application to human cases of tetanus in which both the method of use and the therapeutic action were fully illustrated.

It is now ten years since the first report was made by Meltzer and Auer<sup>3</sup> of the use of intraspinal injections of magnesium sulphate in the treatment of experimental tetanus in monkeys, and while, since that time, our knowledge of the limitations and advantages of its use, as well as the various means of its application, has greatly improved, the clinical world today is by no means of a single mind as to the exact place which this drug should occupy in the routine treatment of the disease in man. The extremes vary from those who use it constantly and often report wonderful results to those who refuse to employ it under any circumstances, preferring the more well-known drugs, such as chloral, opium, etc. These extreme views have become especially prominent during the present European war, in which the disease of tetanus has been a frequent scourge and in which every known method of treatment has found both advocates and opponents. In view of all these facts it has seemed worth while to review in some detail not only the development attained in the employment of magnesium sulphate in the treatment of tetanus, with the various methods used, but also to examine the experimental and clinical evidence for its efficiency, and endeavor thereby to arrive at some fair judgment of the future place which should be accorded to the drug in the treatment of this disease.

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2 The magnesium element is, of course, the active agent and theoretically other salts of this metal, namely, magnesium chlorid, might be employed. In fact, Zuelzer (*Glycerinphosphorsaures Magnesium als Ersatz für Magnesiumsulfat bei der Behandlung des Tetanus*, *Berl klin Wchnschr*, 1915, No 26, p 689), has recently suggested the use of magnesium glycerophosphate instead of the sulphate, claiming that it has the efficacy without the dangers of this latter salt. He recommends 10 cc of a 25 per cent solution given subcutaneously every three or four hours.

3 Meltzer and Auer. *The Effects of Intraspinal Injection of Magnesium Salts on Tetanus*, *Jour Exper Med*, 1906, viii, 692.

## THE INTRASPINAL METHOD

Following the recommendations of Meltzer and Auer,<sup>3</sup> who had experimented with magnesium sulphate on eight monkeys and who reported that early intraspinal injections of the salt were capable of retarding the progress and development of tetanus symptoms, most physicians during the first few years of its general use in tetanus, administered it by lumbar puncture. The proof of its usefulness offered by these earlier workers and clinicians was positive and convincing. Not only in monkeys but also in human beings magnesium sulphate could be injected into the spinal canal in such doses as to preserve the respiratory centers, and yet abolish all the clonic convulsions and tonic contractures of tetanic seizures.

A rather careful survey of all the published reports on the occurrence of tetanus in which sufficient details were furnished to admit of classification shows that 81 cases have been described in which the treatment consisted, in part at least, of intraspinal injections of magnesium sulphate. Blake (Table 2, No 1) in 1906 reported the first case that of a boy of 15, weighing about 115 pounds (or 52 kilos), who after seven days' incubation period developed a severe attack of tetanus. On the fifth day of the disease he received by lumbar puncture 4.5 c.c. of a 25 per cent solution of magnesium sulphate (or 0.024 gm per kilo). The first effects of the salt were noted in less than three hours and in six hours the boy's muscles were so completely relaxed that he could open his mouth and take nourishment. On a return of his symptoms thirty-three hours after the injection, a second dose of 8 c.c. of a 12.5 per cent solution was given by the same route. In all, the boy received five injections, each one being followed by marked relief and being free from any observable injurious results. Tetanus antitoxin was also freely given and the case ended in complete recovery. Blake (Table 2 No 2) in this same article, reported the first failure of this new therapeutic procedure, in a case of Dr Markoe's in which the patient, a boy of 4 years, died twenty-eight hours after the appearance of the first symptoms. The one dose of magnesium sulphate (0.02 gm per kilo) produced only a slight and transitory amelioration of the spasms.

It only would prove tiresome and also would serve no good purpose to repeat the details of these 81 cases. There may, however, be some value in an analysis of the group as a whole. Thus of the 81 patients, 36 died and 45 recovered, a mortality percentage of 44.4. Of those cases having an incubation period of five days or less (Table 1)—a group which embraces the most severe and almost uniformly fatal cases—6 of the 10 patients treated by intraspinal injections died, a mortality of 60 per cent. Here it must be noted that in one of the fatal cases no antitoxin whatsoever was administered and often only

TABLE 1—TETANUS CASES TREATED BY INTRASPINAL INJECTIONS OF MAGNESIUM SULPHATE INCUBATION PERIOD UNDER SIX DAYS

Author	Publication	Incub Days	Quantity $MgSO_4$	Anti toxin*	Result†	Remarks
1 Meltzer and Auer	Jour Exper Med, 1906, VIII, 705	4	1 cc 25% sol to 18 lbs body weight	+	X	Complete relaxation No disturbance of respiration
2 Peck	Reported by Meltzer, 1906	4	1 inj 1 cc 25% sol to 12 kg	+	X	After $MgSO_4$ all symptoms subsided Death 2 hours after antitoxin, intra venous
3 Henry	Internat Clin, 1907, No 17, Ser iv, p 1	3	2 inj 3 cc 25% sol	?	0	Excellent results from $MgSO_4$
4 Rivet, Brébaut and Weil	Tribune méd, Dec. 18, 1909	5	3 inj 10 cc 25% sol	+	0	Retention of urine for 8 days
5 Phillips	Proc Roy Soc. Med, 1909 10, III, 29	3	3 inj 1 cc 25% sol, 1 inj 8 cc 25% sol, 1 inj 8 cc 25% sol	—	X	The last two days $MgSO_4$ had no effect No other treatment given
6 Phillips	Proc Roy Soc. Med, 1909 10, III, 29	1	1 inj 5 cc 25% sol	?	X	Attempted second injection of $MgSO_4$ failed
7 Fox	Med Rec, New York, 1910, lxxviii, 262	5	25 min 25% sol	+	0	$MgSO_4$ delayed until symptoms became serious
8 Fox	Med Rec, New York, 1910, lxxviii, 262	5	1 inj 3 cc. sat sol	+	X	Failure of respiration Washed out subdural space
9 Arnd	Cor Bl f schweiz Aerzte, 1913, xliii, 105	5	5 inj 23 cc 15% sol	+	0	Complicated by pneumonia
10 Strommeyer	München med Wehnschr, 1914, No 28, p 1550	4	1 inj 1 cc 10% sol	?	X	

\* The sign + = antitoxin given, the sign —, antitoxin not given  
† The sign X = death, the sign 0, recovery

one dose of magnesium sulphate was given, sometimes late in the disease. One patient (Meltzer and Auer<sup>3</sup>) died while under the influence of the drug, and in another (Stromeyer, Table 1, No 10) death apparently resulted from respiratory failure and pneumonia two hours after the injection. It is not improbable, however, that most, if not all, of these patients would have died under any circumstances. The number is too small and each case too evidently selected for publication to furnish data on which any certain conclusions may be based. Anders and Morgan,<sup>4</sup> however, in a tabulation of 216 cases collected by them in 1905 present statistics which afford some interesting comparisons (Table 6, Nos 4 and 5). Of 38 patients having an incubation period of five days or less and not receiving antitoxin 36 died, a mortality of 95 per cent.<sup>5</sup> In the cases of 23 patients with similar incubation but treated by antitoxin 17, or 74 per cent, did not recover.

The second group (that given in Table 2) includes 29 cases with an incubation period of six to ten days and a mortality of 48.6 per cent. Anders and Morgan's cases in this group<sup>4</sup> (Table 6, Nos 4 and 5) show 58 who received no antitoxin with 79 per cent mortality. In the 56 cases reported by them in which antitoxin was given 40 patients, or 71 per cent, died. Further reference to Table 6, however, shows that similarly computed end results may show wide variations, which range from 95.6 per cent mortality (Richter) of such patients without antitoxin, to 73.28 per cent (Irons<sup>6</sup>), 54.5 per cent (Chattot<sup>7</sup>), 43.8 (Kohler<sup>8</sup>), and 42 per cent (Lemonnier<sup>9</sup>) when the serum treatment was used.

In the third group (that in Table 3) with incubation periods over ten days, 29 per cent of 24 patients died. Here again Anders and Morgan's results<sup>4</sup> (Table 6, Nos 4 and 5) are significant. In the cases of 18 patients with similar incubation but not receiving serum the mortality was 93 per cent, while of 23 patients treated with antitoxin 35 per cent died. Irons' mortality<sup>6</sup> for this group is 40.5 per cent.

It becomes readily apparent from all these figures as well as examination of the details of the individual cases, not only that antitetanus serum holds a valuable place in the treatment of all cases of tetanus, whatever the incubation period, but also that the administration of magnesium sulphate by intralumbar injections has brought about a

4 Anders and Morgan. Tetanus, Jour Am Med Assn, 1905 xlv, 314.

5 In Richter's series (*Chirurgie des Schussverletzungen im Kriege*, 1877, p 845), a similar group shows a mortality of 96 per cent.

6 Irons. The Treatment of Tetanus by Antitoxin, Jour Am Med Assn, 1914, lvi, 2025.

7 Chattot. Sérothérapie antitétanique. Thèse de Lyon, 1909.

8 Kohler. Zum gegenwärtigen Stand der Serumtherapie des Tetanus, München med Wchnschr, 1898, No 45, p 1429 and No 46 p 1470.

9 Lemonnier. Contribution à l'étude du traitement du tétanos, Thèse de Paris, 1901.

TABLE 2—TETANUS CASES TREATED BY INTRASPINAL INJECTIONS OF MAGNESIUM SULPHATE INCUBATION SIN TO TEN DAYS

Author	Publication	Incub Days	Quantity $MgSO_4$	Intoxi <sup>n</sup> Results	Remarks
1 Blake	Surg, Gynec and Obst, 1906, II, 511	7	2 inj 15 cc 25% sol, 3 inj 5 cc 12.5% sol	0	No injurious results from $MgSO_4$
2 Blake	Surg, Gynec and Obst, 1906, II, 541	7	1 inj 15 cc 25% sol	1	Return of convulsions within 1 hour of injection
3 Logan	Jour Am Med Assn, 1906, XLVI, 1592	9	1 inj 4 cc 25% sol	+	Profuse bronchorrhea
4 Henry	Internat Clin, 1907, No 17, Ser IV, p 1	7	1 inj 6 cc 25% sol	?	One hour after injection entirely relaxed
5 Henry	Internat Clin, 1907, No 17, Ser IV, p 1	6	1 inj 2.5 cc 25% sol, 1 inj 2 cc 20% sol	0	Rise of temperature after both injections
6 Raymond and Doury	Bull et mem Soc med d hôp de Paris, 1908, XXV, 350	6	1 inj 6 cc 25% sol, 1 inj 1 cc 25% sol, 1 inj 3 cc 25% sol	+	Recommends $MgSO_4$ highly
7 Powers	Med Rec, New York, 1908, LVIII, 140	10	2 inj 2 cc 25% sol	+	Complete relaxation but patient complained of headache
8 Winthrop	South Med Jour, 1909, II, 916	9	3 inj 3 cc 25% sol, 1 inj 3 cc 25% sol	0	
9 Willets	Penn Med Jour, 1909 10, XLIII, 803	7	Injections given for 1 week	+	Cyanosis after $MgSO_4$ but was never dangerous
10 Tanton	Progrès med, 1909, XXV, 35	8	2 inj 12.15 cc 1% sol, 1 inj 3 cc 25% sol	+	Relaxation of muscles after $MgSO_4$
11 Phillips	Proc Roy Soc Med, 1909 10, III, 39	7	1 inj 2.5 cc 25% sol, 2 inj 3 cc 25% sol, 13 inj 3.5 cc 25% sol	+	One injection given daily No bad effects
12 Phillips	Proc Roy Soc Med, 1909 10, III, 39	7	2 inj 5 cc 25% sol	+	
13 Phillips	Proc Roy Soc Med, 1909 10 III, 39	7	5 inj 2 cc 25% sol	+	Gave $MgSO_4$ because antitoxin and phenol showed no effect

14 Hirsch	Surg, Gynec and Obst, 1909, No 1, p 76	8	6 inj 5 cc 25% sol	+	0	After first injection rigidity of legs did not return
15 Hirsch	Surg, Gynec and Obst, 1909, ix, 145	6	1 inj 3 cc 25% sol	+	X	Death from paralysis of heart
16 Malanink	Wien, med Wchnschr, 1909, No 27, p 1530	9	2 inj 2 cc 25% sol	?	X	
17 Holman	Northwestern Lancet, 1911, xxi, 103	10	2 inj 5 cc 25% sol	+	X	Failure of respiration after second injection
19 Pett	Thèse de Paris, 1912	9	2 inj 3 cc 25% sol	+	X	Good results from MgSO <sub>4</sub>
19 Kocher	Cor Bl f schweiz Aerzte, 1912, No 26, p 919	7	6 inj 3.5 cc 25% sol	+	0	After sixth injection, failure of respiration Tracheotomy
20 Kocher	Cor Bl f schweiz Aerzte, 1912, No 26, p 919	10	14 inj 5.10 cc 15% sol	+	0	After 3 gm MgSO <sub>4</sub> , loss of consciousness, cyanosis
21 Kocher	Cor Bl f schweiz Aerzte, 1913, No 4, p 97	8	1 inj 6.10 cc 15% sol	+	0	After 3.5 gm MgSO <sub>4</sub> within 24 hours, failure of respiration, tracheotomy
22 Kocher	Cor Bl f schweiz Aerzte, 1913, No 4, p 97	9	6 inj 2.5.5 cc 15% sol	+	X	Failure of respiration, tracheotomy death from heart failure
23 Schante	Tidsschr v Geneesk, 1914, li, 1839	10	1 inj 10 cc 10% sol	+	0	
24 Standler	Berl klin Wchnschr, 1914, No 1, p 109, No 3, p 15	8	5 inj 2 cc 15% sol	+	0	Several times severe collapse after MgSO <sub>4</sub>
25 Stromeyer	München med Wchnschr, 1914, No 28, p 1556	6	1 inj 8 cc 15% sol, 1 inj 8 cc 25% sol	?	0	No failure of respiration
26 Stromeyer	München med Wchnschr, 1914, No 28, p 1556	10	1 inj 8 cc 15% sol	?	X	Died four days after injection from heart failure
27 Stromeyer	München med Wchnschr, 1914, No 28, p 1556	6	1 inj 8 cc 15% sol	?	X	Died day after MgSO <sub>4</sub> from heart failure
28 Goldschmidt	Berl klin Wchnschr, 1915, No 10, p 229	7	1 inj 2 cc 15% sol	+	X	MgSO <sub>4</sub> without effect
29 Bruce	Lancet, London, 1915, li, 991	6	3 inj 2 cc 25% sol	+	0	

\* The sign + = antitoxin given, the sign —, antitoxin not given

† The sign X = death, the sign 0, recovery



TABLE 3—TETANUS CASES TREATED BY INTRASPINAL INJECTIONS OF MAGNESIUM SULPHATE INCUBATION PERIOD OVER TEN DAYS

Author	Publication	Incub Days	Quantity MgSO <sub>4</sub>	Antitoxin*	Result	Remarks
1 Logan	Jour Am Med Assn, 1906, xvi, 1502	17	2 inj 1 cc 25% sol	+	N	MgSO <sub>4</sub> of little value
2 Franke	Zentralbl f Inn Med, 1907, No 14, p 345	12	1 inj 12 cc 25% sol, 2 inj 2 cc 25% sol	—	0	Relief from MgSO <sub>4</sub> when other narcotics had failed
3 Henry	Internat Clin, 1907, No 17, Ser iv, p 1	21	2 inj 6 cc 25% sol	+	X	"It is very much a question whether the MgSO <sub>4</sub> did not contribute to the patient's death"
4 Griffon and Llan	Bull et mem Soc méd d hôp de Paris, 1908, No 27, p 190	14	2 inj 2 cc 25% sol	+	0	Recommend, MgSO <sub>4</sub> highly
5 Willets	Penn Med Jour, 1909 10, viii, 863	13	6 inj 25 cc 25% sol	+	0	Relaxation of all muscles after MgSO <sub>4</sub>
6 Phillips	Proc Roy Soc Med, 1909 10, iii, 39	39	5 inj 2 cc 25% sol, 3 inj 25 cc 25% sol, 1 inj 3 cc 25% sol	+	0	
7 Malanink	Wien med Wehnschr, 1909, No 27, p 1550	80	1 cc 25% sol every 2 days 5 cc 25% sol every 3 days	?	0	Good symptomatic influence from MgSO <sub>4</sub>
8 Malanink	Wien med Wehnschr, 1909, No 27, p 1550	14	5 cc 25% sol every 2 days	—	0	
9 Malanink	Wien med Wehnschr, 1909, No 27	11	3 inj 2 cc 25% sol	+	X	Severe case Death on fourth day
10 Goepf and Esbner	Penn Med Jour 1909 10, viii, 861	20	12 inj 2 cc 25% sol	+	0	
11 Fox	Med Rec, New York, 1910, lxxviii, 720	11	1 inj 2 cc 25% sol	+	0	"Outcome dubious until MgSO <sub>4</sub> was given"
12 Johnson	Brit Med Jour, 1910, ii, 457	23	2 inj 45 min 25% sol, 2 inj 1 dr	+	0	Complete relaxation after each injection

12 Bertucat	Lohre med, 1911, 115	60	3 injections	+	0	Chloral and morphin without effect MgSO <sub>4</sub> with good results
14 Holman	Northwestern Lancet, 1911, 111, 163	19	9 inj 10 cc 12.5% sol, 10 inj 5 cc 25% sol	+	0	
15 Smithson	Brit Med Jour, 1912, 1, 181	13	1 inj 1 cc 25% sol	+	X	For six hours after injection complete relaxation, then high fever with violent spasms
16 Kocher	Cor Bl f Schweiz Aerzte, 1912, No 26, p 219	26	7 inj 2.5 cc 25% sol	+	0	
17 Kocher	Cor Bl f Schweiz Aerzte, 1913, No 4, p 37	28	6 inj 6 10 cc 25% sol	—	0	Failure of respiration, tracheotomy
18 Tilly	Brit Med Jour 1913, 1, 1104	20 27	3 inj 3 cc 25% sol	+	0	
19 Spannuth	Med Klin, 1914, No 46, p 1683	11	6 inj 25% sol 0.02 gm to 1 kg	—	0	
20 Schoute	Tijdschr v Geneesk, 1914, II, 1839	11	2 inj 10 cc 10% sol	+	X	
21 Schoute	Tijdschr v Geneesk, 1914, II, 1839	12	3 inj 10 cc 10% sol	—	0	
22 Vuillet	Rev mcd de la Suisse, 1914, No 3, p 185	14	2 inj 6 cc 15% sol	?	X	Warns that MgSO <sub>4</sub> is a two edged sword and may do more harm than good
23 Stromeyer	Munchen med Wehnsehr, 1914, No 28, p 1536	11	1 inj 8 cc 15% sol	?	X	Thinks he gave too small doses
24 Mertens	Munchen med Wehnsehr, 1915, No 17, p 534	16	1 inj 1.5 min 10 cc fluid	+	0	"MgSO <sub>4</sub> intraspinally by no means a harmless remedy"

\* The sign 1 = antitoxin given, the sign —, antitoxin not given

† The sign X = death, the sign 0, recovery

LE 4--TETANUS CASES TREATED BY INTRASPINAL INJECTIONS OF MAGNESIUM SULPHATE INCUBATION PERIOD UNKNOWN

Author	Publication	Quantity MgSO <sub>4</sub>	Antitoxin*	Result	Remarks
1 Robinson	Jour Am Med Assn , 1907, xxix, 493	1 inj 3 cc 25% sol , 1 inj 3.5 cc 25% sol , 1 inj 4 cc 25% sol	—	0	Improvement after MgSO <sub>4</sub>
2 Muller	Am Jour Med Sc , 1908, cxxxvi, 781	11 inj 2.5 cc 25% sol	+	0	Recommends treatment highly
3 Willets	Penn Med Jour , 1909, viii, 863	1 inj 3 cc 25% sol , 2 inj 4 cc 25% sol	?	0	Artificial respiration necessary for six hours after third injection
4 Rieurd and Dreuet	Bull et mem Soc méd d hop de Paris, 1909, xxvi, 189	1 inj 3 cc 25% sol	?	X	Relief for 24 hours, but spasms returned, death 12 hours later
5 Roger and Rives	Province méd Jour , 1909, xx, 236	1 inj 2 cc 25% sol	+	X	MgSO <sub>4</sub> afforded some slight relief
6 Roger and Rives	Province med Jour , 1909, xx, 236	1 inj 20 cc 5% sol	+	X	Patient died 26 hours after appearance of first symptoms
7 River, Bricout and Weil	Tribune med , Dec 18, 1908, p 805	3 inj 10 cc 25% sol	+	0	Retention of urine for 10 days
8 Popesco and Protoposco	Bull et mem Soc méd d hop de Paris, May, 1909, p 774	1 inj 4 cc 25% sol , 3 inj 2 cc 25% sol	+	0	One hour after each injection MgSO <sub>4</sub> complete relaxation
9 Phillips	Proc Roy Soc Med , 1909 10, III, 39	6 inj 2 cc 25% sol	+	0	Gave one injection daily Good results
10 Netter	Bull et mem Soc med d hôp de Paris, January, 1909, xxvi, p 151	?	?	X	MgSO <sub>4</sub> could not prevent recurrence of spasms or death
11 Debre	Bull et mem Soc méd d hôp de Paris 1909, Ser 3, p 139	1 inj 2 cc 25% sol	+	X	Excellent effect for 8 hours then return of symptoms and death
12 Aubry and Lerat	Gaz med de Nantes, May 1, 1909, p 350	3 inj 25% sol	?	0	MgSO <sub>4</sub> produced positive aneliorition
13 Lepornant and Josset Moure	Bull et mem Soc méd d hop de Paris 1909, xxvi, 131	2 inj 25% sol	+	X	No modification of symptoms after MgSO <sub>4</sub>
14 Page	Proc Roy Soc Med , Jan 25, 1910, p 51	1 inj 5 cc 25% sol	?	X	Respiratory failure "Very dangerous drug"
15 Gardner	Austral Med Jour , 1911, xvi, 265	1 inj 3 cc 25% sol , 11 inj 1 cc 25% sol , 2 inj 2.5 cc 25% sol	+	0	Gave MgSO <sub>4</sub> at 18 hour intervals
16 Smithson	Brit Med Jour , 1912, I, 181	1 inj 2.5 cc 25% sol	+	X	Failure of respiration but no recurrence of convulsions
17 Palassee	Province med , 1912, No 31, p 375	1 inj 5 cc 25% sol	—	0	High fever and disturbances of circulation after MgSO <sub>4</sub>
18 Stadler	Berl klin Wchnsehr , 1914, No 1, p 15	3 inj 10.5 and 1 cc 15% sol	+	X	Death from heart failure without asphyxia or convulsions

\* The sign + = antitoxin given, the sign —, antitoxin not given  
+ The sign X = death, the sign 0, recovery

definitely certain, even if small, decrease, in the percentage of deaths from tetanus, as well as causing an undoubted diminution in the agony and suffering which accompany the spasmodic seizures of this disease. But our conclusions must not rest here. Further evidence remains to be examined.

#### THE SUBCUTANEOUS METHOD

In 1907 Greely published a report of the first case to be treated by subcutaneous injections of magnesium sulphate. The salt was given in very dilute solutions (for a child of 2 years, 2 drams to a pint or about 0.57 gm per kilo) and Greely was unable to determine whether the good results obtained should be attributed "to a dilution of the poisons and an increase in their elimination, to a neutralizing action of the magnesium sulphate on the toxins of the tetanus bacillus, or to its antagonizing effect on the nerve centers."<sup>10</sup>

Meltzer<sup>11</sup> had previously called attention to the efficacy of the subcutaneous method, as well as that of the more rapidly absorbable intramuscular injection.<sup>12</sup>

Lyon (Table 5, No. 3) in the following year added another successful case, and both Hessert<sup>13</sup> and Parker<sup>14</sup> reported recoveries obtained in which the treatment, in addition to antitoxin, consisted of alternating intraspinal and subcutaneous injections of magnesium sulphate. In a comparison by Stadler,<sup>15</sup> 1914, of those cases treated by intraspinal and those by subcutaneous injections of the salt, he also noted the apparently more favorable results obtained by the latter method.

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10 Greely is not the only one who has administered the salt under the possible presumption that it might have a specific effect on the toxin and therefore prove a substitute for antitetanus serum. Experiments on animals were carried out, among others by Stadler, Camus (*Traitement du tétanos par le sulfate de magnésie, par l'acide phenique, par le serum antitetanique*, *Compt rend Soc de biol*, 1912, lxxii, 109), and McClintock and Hutchings (*The Treatment of Tetanus*, *Jour Infect Dis*, 1913, xiii, 309), with a view of establishing its worth as a *cure* for the tetanus infection. It seems almost needless to add that this presumption rests on no solid foundation of either experimental or clinical proof. Meltzer and his pupils have never claimed that the drug could do more for tetanus victims than to relax the tetanized muscles, thus conserving the patient's strength and gaining time not only for the neutralization of all free toxin by antitoxin but also for the recovery of the nerve centers already affected by their union with toxic elements.

11 Meltzer and Auer. *General Anesthesia after Subcutaneous Injections of Magnesium Sulphate*, *Am Jour Physiol*, 1906, xiv, 366. Meltzer and Auer. *The Antagonistic Action of Calcium on the Inhibitory Effects of Magnesium*, *Am Jour Physiol*, 1908, xxi, No. 4, p. 400.

12 This latter method has never been widely employed for administering magnesium salts, probably because of the painfulness of the treatment.

13 Hessert. *The Treatment of Tetanus*, *Surg, Gynec and Obst*, 1909, ix, 145.

14 Parker. *Treatment of Tetanus with Magnesium Sulphate*, *Jour Am Med Assn*, 1912, lviii, 1746.

15 Stadler. *Die Magnesiumsulfatbehandlung des Tetanus*, *Berl klin Wchnschr*, 1914, No. 1, p. 15, and No. 3, p. 109.

TABLE 5—TETANUS CASES TREATED BY SUBCUTANEOUS INJECTIONS OF MAGNESIUM SULPHATE

Author	Publication	Incub Days	Quantity MgSO <sub>4</sub>	Antitoxin	Result	Remarks
1 Greely	Jour Am Med Assn, 1907, vii, 910	10	2 inj 7.5 gm	+	0	
2 Greely	Jour Am Med Assn, 1907, vii, 910	28	3 inj 3.5 gm	—	0	Very severe case
3 Lyon	Jour Am Med Assn, 1908, i, 1688	8	5 inj 2 dr MgSO <sub>4</sub> in 4 oz water	?	0	MgSO <sub>4</sub> relaxed muscles to marked degree
4 Paterson	Lancet, London, April 2, 1910, p 922	14	10-20 cc 10% sol every 4 hours	—	0	Injections painful but effect of MgSO <sub>4</sub> appeared very quickly
5 Parker	Jour Am Med Assn, 1912, lviii, 1716	7	9 dr 25% sol every 2 hrs first day, 8 dr 25% sol daily for one week	+	0	No toxic effects from MgSO <sub>4</sub>
6 Parker	Jour Am Med Assn, 1912, lviii, 1716	10	3 inj 10 dr 25% sol	+	0	MgSO <sub>4</sub> given daily for 3 days
7 Mielke	Therap Monatsh, 1914, No 4, p 259	?	15 cc 20% sol for 10 days	+	0	Child did not complain of local pain from injections
8 Czerny	Deutsch med Wehnschr, 1914, No 44, p 1905	10	1 inj 10 cc 25% sol	+	✓	Death from pneumonia after tetanic spasms had ceased
9 Czerny	Deutsch med Wehnschr, 1914, No 41, p 1905	13	6 inj 15 cc 25% sol	+	0	Daily injections for 6 days
10 Czerny	Deutsch med Wehnschr, 1914, No 44, p 1905	9	10 cc 25% sol daily	+	0	MgSO <sub>4</sub> first followed by improvement later no effect
11 Roznowski	Ztschr f Wundarzte u Geburtsh, 1914, kv, 115	1	60 inj 5-10 cc 25% sol	+	0	From 60 injections only one abscess developed
12 Heddaus	München med Wehnschr, 1914, No 13, 2186	9	10 gm daily 25% sol	+	0	Improvement after first injection, later no effect
13 Syring	Deutsch med Wehnschr, 1914, No 40, p 2029	20	25 inj 10 cc 10% sol	—	0	No bad effects from MgSO <sub>4</sub>
14 Arzt	Wien klin Wehnschr, 1914, No 52, p 1033	6	9 inj 1 cc 30% sol	+	0	

15 Arzt	Wien klin Wehnschr, 1914, No 52, p 1633	6	† Inj 5 c c 30% sol	+	0	
16 Arzt	Wien klin Wehnschr, 1914, No 52, p 1633	12	† 5 c c 30% sol	+	0	
17 Arzt	Wien klin Wehnschr, 1914, No 52, p 1633	12	† 5 c c 30% sol	+	0	
18 Dreyfus and Unger	München med Wehnschr, 1914, No 51, p 2417	67	o Inj 5 c c 25% sol	+	0	
19 Dreyfus and Unger	München med Wehnschr, 1914, No 51, p 2417	6	3 Inj 5 gm 25% sol	+	0	
20 Dreyfus and Unger	München med Wehnschr, 1914, No 51, p 2417	8	6 Inj 5 gm 25% sol	+	0	
21 Czerny	Deutsch med Wehnschr, 1914, No 40, p 1806	?	3 Inj daily 10 c c 25% sol	+	0	
22 Falk	Deutsch med Wehnschr, 1914, xl, 1689	?	In 24 hours † gm 10 15% sol	?	0	After injections, respiration failure 20 minutes
23 Falk	Deutsch med Wehnschr, 1914, xl, 1689	?	In 24 hours 3.6 gm 10 15% sol	?	0	Continued MgSO <sub>4</sub> for 10 days
24 Falk	Deutsch med Wehnschr, 1914, xl, 1689	?	In 24 hours 2.1 gm 10-15% sol	?	0	Light case, no disturbance of respirations
25 Usener	München med Wehnschr, 1914, No 48, p 2223	?	15 c c 25% sol every 2 hrs	?	0	Gave as much as 40 gm MgSO <sub>4</sub> a day
26 Usener	München med Wehnschr, 1914, No 48, p 2223	?	15 c c 40-50% sol every 2 hours	?	0	Great success
27 Schlesinger	Wien klin Wehnschr, 1914, No 48, p 1553	?	20 c c 25% sol 3 times daily	?	0	Spasms controlled in ½ to ¾ hour after injection
28 Reingruber	Therap monatsh, 1915, xxix, 148	?	20-25% sol every 2-3 hrs until 20-30 gm of sol in 24 hrs	—	0	MgSO <sub>4</sub> had instant effect upon spasms

\* The sign + = antitoxin given, the sign —, antitoxin not given

† The sign X = death, the sign 0, recovery

Mielke<sup>16</sup> in treating a girl of less than 6 years, for sixteen days gave each day 3 gm (15 c c of a 20 per cent solution) of magnesium sulphate in divided doses about four hours apart. The doses averaged from 0.5 to 0.7 gm per kilo of body weight. Far from causing the child painful effects, she was afforded such relief from the tetanic spasms that frequently she pleaded that the interval between the injections be shortened.

The literature gives details of 29 cases (Table 5) in which the patients received, in addition to antitoxin and other treatment, magnesium sulphate administered exclusively by subcutaneous injections. Only one patient (Roznowski, Table 5, No. 11), who recovered, gave an incubation period under six days. In the 12 cases beginning on the sixth to tenth days, inclusive, only one patient died, a mortality of 8.3 per cent as compared with 48.6 per cent for the same group treated by the intralumbar method. Of the 6 patients having incubation period above ten days and the 9 patients for whom this period is not stated, all recovered, giving a mortality for the entire group of only 3.7 per cent.<sup>17</sup>

Even admitting that the total number of cases is far too small, that the list is also obviously composed of selected successes, and that the more severe cases of shorter incubation time are noticeable for their absence, the result, nevertheless, is imposing and worthy of the most earnest consideration.

#### THE INTRAVENOUS METHOD

A third method for the administration of magnesium salts in cases of tetanus deserves mention, more perhaps because of its theoretical than because of its practical bearing. Straub,<sup>18</sup> whose earlier work with magnesium salts was devoted to pharmacological researches on their modes of action, was impressed in experiments with the subcutaneous injections of magnesium sulphate with the short, as well as the variable, duration of the effects obtained by this method. To illustrate, he noted that in a rabbit weighing 2 kilos, 10 c c of a 25 per cent solution, given in a single dose under the skin was sufficient to produce a maximum therapeutic effect lasting about twenty minutes. If, however, that amount was divided into four equal doses injected

16 Mielke. *Beitrag zur Behandlung von Tetanus mit Magnesiumsulfuricum*, *Therap. Monatsh.*, 1914, No. 4, p. 259.

17 The one patient who died (Czerny. *Zur Therapie des Tetanus*, *Deutsch. med. Wchnschr.*, 1914, No. 44, p. 1905), had practically completely recovered from tetanus symptoms and death on the twelfth day was said to have been caused by pneumonia.

18 Straub. *Experimentelle Untersuchung über Wesen und Aussicht der Tetanustherapie mit Magnesiumsulfat*, *München med. Wchnschr.*, 1915, No. 1, p. 25. *Tetanustherapie mit Magnesiumsulfat*, *München med. Wchnschr.*, 1915, No. 10, p. 341.

TABLE 6—COLLECTED CASES WITH COMPARISON OF TOTALS AND MORTALITY PERCENTAGES AT VARYING INCUBATION PERIODS

Reported by	Treatment	Total Cases	Incubation Under 6 Days			Incubation 6 to 10 Days			Incubation Over 10 Days		
			Cases	Per Cent	Per Cent	Cases	Per Cent	Per Cent	Cases	Per Cent	Per Cent
1 Author	MgSO <sub>4</sub> intraspinal	21	10	48	60	29	136	29	25	80	29
2 Author	MgSO <sub>4</sub> subcutaneous	27		37		12	83				
3 Richter	Without serum	214	25	880	96	91	956		18	80	
4 Anders and Morgan	Without serum	114	28	780	95	58	790		23	85	
5 Anders and Morgan	With serum	102	23	637	71	56	710		69	105	
6 Irons	With serum	225		857		131	738				
7 Kohler	With serum					12	138				
8 Chattot	With serum					110	545				
9 Lemonnier	With serum	176				?	420		?	176	



at fifteen-minute intervals, no effect whatsoever was seen, while, on the other hand, if the four doses were injected into four different places at the same time the animal would die in a few minutes. From this he concluded that the action of magnesium sulphate follows solely from its rapid absorption into the circulation and that the intensity of this action is directly proportional to the amount of concentration which the salt reaches in the blood stream. As the kidneys are the main route for the elimination of the drug, he was able to further establish his contention by measuring the rate of excretion in the urine compared with the duration of the effects. Naturally, the rate of absorption from subcutaneous injections varies within wide limits depending upon site, amount, concentration, etc., and hence the reason for the varying intensities and durations of action.

The logical application of these statements is obvious and Straub<sup>18</sup> proceeded to test it by the continuous injection into the blood of animals of a magnesium sulphate solution in such concentration that the pharmacological effect would be constantly maintained and at such a rate as would approximately equal that of its elimination in the urine. As these tests seemed to demonstrate the value of the method, it remained only to test its application on actual cases of human tetanus, a proceeding which a few months later (1915) Straub was able to report. Four patients were treated with a continuous intravenous flow of a 3 per cent solution of magnesium sulphate. In the first (a case of light local tetanus) a rate of 100 cc in twelve minutes was continued for one hour with no effect. The rate was then increased six times, so that 100 cc entered the circulation every two minutes, and typical and satisfactory effects were observed. This observation was repeated on the following day with similar effect and apparently demonstrated that the action of the salt depended solely on its concentration in the blood. The next trial was on a severe case of tetanus in which the first symptoms had appeared eight days after fracture of the arm caused by a bursting shell. The mouth could not be opened, speech was difficult, swallowing impossible, and painful paroxysms of the neck muscles were frequent. After the inflow of a 3 per cent solution at the rate of 25 cc every two minutes, all pain, spasms, and paroxysms disappeared and the patient could talk and drink fluids. One hour after stopping the flow the symptoms began gradually to reappear, to be again controlled by another injection. The interesting observation was made that the muscles affected by the spasms were acted on before the normal muscles and that doses far too small to produce any disturbance of the respiratory centers were sufficiently effective. As the constantly continuous flow proved too great a burden on the circulation (kidneys?), the intermittent method of application was found most suitable. In at least one case the canula was fastened into the vein

and the solution allowed to enter whenever the condition of the patient demanded, for example, for nourishment, changing of dressings, sleep, or too severe muscular spasms. In the case of one patient who recovered this procedure was continued for eight days. The dangers of thrombosis were apparently counteracted by the coagulation-inhibiting properties of the magnesium solution and examination of the veins on necropsy failed to disclose either thrombus or demonstrable injury to the vein wall. Chemical examination of the urine showed that the excreted amounts of magnesium were about equal to the intake.

The actual application of Straub's method in severe cases of tetanus proved disappointing as far as its influence on the eventual outcome of the disease was concerned and its manifest dangers resulted in a suspended judgment as to its true worth<sup>19</sup>

These experiments have been described in some detail because they undoubtedly illustrate in a very forceful manner not only the theoretical considerations governing the action of this salt but also some of the difficulties which must be encountered in its use, as well as the evident value of its properties in the routine treatment of tetanus.

#### ACCIDENTS IN THE USE OF THE SALT

As stated above, it must be admitted that, in general, narcotic, anesthetic, or antispasmodic drugs depend on a toxic action for their useful effects, and such effects are always obtained at a distinct cost to part or all of the vital functions of the body. In the use of magnesium salts in tetanus there is considerable evidence which leads to the belief that these are no exception to this general rule. In short, there have been shown, both experimentally and in cases of tetanus, distinct dangers associated with the injections of magnesium sulphate, which dangers must be regarded as an important factor in determining the rightful position which should be accorded to the salt as a remedy. For example, when an overdose of magnesium sulphate in solution is injected rapidly into the blood stream, almost instantaneous death sometimes occurs. This effect is probably brought about by its direct action in concentrated form either on the heart itself or on the cardiac centers of the spinal cord. At any rate the heart suddenly ceases to beat, even before cessation of respiration. As a rule, this misfortune follows only a huge or highly concentrated dose and takes place almost solely as the result of intravenous administration. That such is not always the case, however, was demonstrated on several occasions in a

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19 In this connection it should be noted that Meltzer (Meltzer and Auer *Einiges zur Physiologie und Pharmakologie des Magnesium und Kalzium*, Deutsch med Wchnschr, 1909, No 45, p 196), distinctly states that the use of magnesium sulphate in tetanus by intravenous injections should not be considered ("Intravenöse Einspritzungen sollen beim Menschen gar nicht in Betracht kommen")

series of experiments in which I was endeavoring to substitute intra-abdominal for intravenous injections of magnesium sulphate in the treatment of experimental tetanus in animals. Large and concentrated doses often led to sudden interruption of the heart's action and this effect was produced almost as rapidly by the intraperitoneal as by the intravenous route. This accident was never observed to follow subcutaneous injections but some reports on patients treated by the intralumbar method suggest strongly that here also there may be a possible danger to the cardiac apparatus. While this accident, when it does occur, has no known remedy, death taking place almost immediately, it must be admitted that, with ordinary precautions, it is not to be expected. Indeed, Meltzer has steadily denied its possibility, asserting that the salt's dangerous action is exerted mainly if not solely on the respiratory centers. However, the above-mentioned facts render necessary further study on this point and in the meantime its use in cases of known cardiac weakness certainly deserves some caution.

The most important and frequent accident resulting from the use of magnesium salts is interference with respiration, that is, respiratory paralysis. This effect apparently is produced by the salt's acting directly on the centers of respiration, and while Meltzer, among others, early demonstrated that tetanized muscles could be relaxed by appropriate doses without endangering the respiration, nevertheless the danger was such a real one that the need for some antidote became at once apparent. Long before magnesium sulphate was proposed for the treatment of tetanus the antagonistic action between the salts of magnesium and calcium had been observed (Loeb<sup>20</sup>). Later Meltzer showed by experiments on rabbits that calcium can remove the inhibiting effect of magnesium. He administered subcutaneously 7 c c of a 25 per cent solution of magnesium sulphate and when the animal was in deep anesthesia and the muscles completely relaxed, injected slowly into the ear vein 6 to 8 c c of a 3 per cent solution of calcium chloride. In a few moments the respirations became deeper and more rapid, the lid reflex reappeared and the animal attempted to get up, often before the injection was entirely finished. Several minutes later the animal was apparently entirely normal. This effect ensued even when the respirations had entirely ceased, in fact as long as the heart action remained intact. The same result was obtained in experiments on monkeys, and occurred no matter whether the magnesium sulphate had been injected subcutaneously, intramuscularly, or intravenously.

This neutralizing action was not so apparent when the magnesium salt was applied directly to the medulla or the nerve trunks or injected into the subarachnoid space. Hence, for combating its effects after

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20 Loeb Jour Biol Chem, 1905-1906, 1, 427

intralumbar injections it was suggested that washing out the subarachnoidal space with physiological salt solution would rapidly relieve the depressent action of the magnesium. Physostigmin was also shown by Joseph and Meltzer<sup>21</sup> to act as an efficient remedy against the threatened respiratory depression of magnesium salts.

Kocher,<sup>22</sup> who was an early champion of the use of magnesium sulphate in tetanus, experienced considerable difficulty with this complication. In some of his early cases he was compelled to perform tracheotomy and even proposed this procedure in severe cases as a routine precautionary measure. He also tested the effect of physostigmin, washing out the intralumbar space with salt solution and tracheal insufflation. He was finally led to recommend that when the salt was injected into the spinal canal, the patient be elevated to a sitting or half reclining position to prevent its early diffusion to the vital centers. Kocher later (1914) abandoned entirely the intralumbar method in children but intimated that in adults he feared the effect on the heart's action of subcutaneous injections although admitting that in general they were "much milder and less dangerous" than lumbar injections and overdoses could be easily controlled by the use of 5 per cent solutions of calcium chlorid, or by physostigmin. He proposed a well-known modification of the tracheal insufflation method devised by Meltzer† to aid artificial respiration. It is of interest to note that after a large and varied experience with its use Kocher concluded that in magnesium sulphate we have a most important remedy for preventing the fatal outcome of severe cases of tetanus. Falk<sup>23</sup> among others tested the efficacy of calcium chlorid in respiratory paralysis which appeared in two of his cases and found prompt betterment following *intramuscular* injection of 5 c.c. of a 5 per cent solution.

I have dwelt on this complication at some length because it constitutes the most serious objection to the use of magnesium sulphate in tetanus. Moreover, this danger seems to be exaggerated when the salt is administered intralumbarly not only because of the possibility of directly diffusing toward higher centers in too great concentration but also because remedies such as calcium chlorid or physostigmin are not so efficient under these circumstances. With subcutaneous injec-

21 Joseph and Meltzer. The Life-Saving Action of Physostigmin in Poisoning by Magnesium Salts, *Jour. Pharmacol. and Exper. Therap.*, 1909, 1, No. 3, p. 369.

22 Kocher. Erfolge einer neuen Behandlungsmethode bei Tetanus, *Cor-Bis f. Schweiz. Aerzte*, 1912, No. 26, p. 919. Weitere Beobachtungen über die Heilung des Tetanus mit Magnesiumsulfat, *Cor-Bis f. Schweiz. Aerzte*, 1913, No. 4, p. 97.

† Meltzer. Pharyngeal Insufflation—A Simple Method of Artificial Respiration, *Studies from the Rockefeller Inst.*, 1913, xvi, No. 6, p. 421.

23 Falk. Zur Behandlung des Tetanus mit subkutanen Magnesiuminjektionen, *Deutsch. med. Wchnschr.*, 1914, xl, 1689.

tions, when respirations become embarrassed we are not so helpless. Subcutaneous, intramuscular, or even intravenous injections of calcium chloride in 5 per cent solution give prompt and often complete relief. Physostigmin and artificial respiration<sup>24</sup> may also prove efficacious. However, the danger hovers near in every case in which the therapeutic limit is reached and as this limit and the maximum desired effect are often nearly identical, it becomes necessary to watch these patients very carefully after the administration of large doses and make preparations in advance to rapidly administer measures of relief when needed.

The remaining complications cannot be considered as of major importance, but they should be kept in mind and, when possible, prevented. Retention of urine, supposed to be caused by paralysis of the muscles, has often been observed, among others, by Kocher<sup>22</sup> (Table 2, Nos 19, 20, 21, and 22, Table 3, Nos 16 and 17), Rivet, Bricout, and Weill<sup>25</sup>. Kocher suggested that the administration of physiological saline under the skin would relieve this condition and, aside from the occasional necessity of catheterization no serious results have been reported. In my experiments with animals this complication has not been noted.

Another objection often raised, especially to subcutaneous injections of the salt, is the supposed painfulness. The evidence in this respect varies. Stadler investigated the subject by making injections into his own tissues of solutions of varying strength. He tried 5.5 per cent (isotonic), 11 per cent, 22 per cent, 35 per cent, and 50 per cent solutions and found that, while the 5.5 per cent and 11 per cent solutions were less immediately irritating but were later followed by pain, the momentary pain of the stronger mixtures (22 to 50 per cent) on the other hand, completely disappeared in a short time. He therefore recommended 30 to 40 per cent solutions, adding that the smaller volume of these injections was in favor of their employment. Mielke<sup>16</sup> also recommended the employment of more concentrated solutions as being less painful. He further suggested the preliminary administration of chloral for the purpose of lessening pain and also to prevent the occurrence of muscular paroxysms during the injections. Falk<sup>23</sup> thought the solution better borne and less painful in dilutions from 10 to 25 per cent. He, however, warned against the painfulness of the injections and advised preliminary small injections of morphin.

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24 Willets (The Treatment of Tetanus with Subarachnoid Injections of Magnesium Sulphate, *Pennsylvania Med Jour* 1909-10, xiii, 863), in one of his cases, used artificial respiration for six hours with final recovery. He believes such attempts are often abandoned too soon.

25 Rivet, Bricout, et Weill. Deux cas de tétanos traités par la sérothérapie le chloral et les injections intrarachidiennes de sulfate de magnésie, *Tribune méd*, Paris, Dec 18, 1909, p 805.

or novocain Wiesel<sup>26</sup> also preceded each injection by novocain to relieve the pain On the other hand, Roznowski (Table 5, No 11) gave his patient 60 subcutaneous injections, and, except for the development of an abscess after one of the treatments, no pain was felt at the local point of injection

On the whole there is little doubt that the injections, especially subcutaneous, are apt to be painful This, however, can be readily controlled by local anesthetics The concentrated solutions are probably best borne, although in Greely's cases, where a less than 2 per cent solution was used, no mention is made of distress at the point of injection

There has been little attention devoted to studies of the actual lesions which may result from the presence of the salt in the subcutaneous or intramuscular tissues Abscesses and occasional sloughing and gangrene are mentioned, but the absence of secondary infection in these cases was not demonstrated Reingruber<sup>27</sup> mentions experiments of Ahrens in which comparisons were made in guinea-pigs of the effects of subcutaneous injections of magnesium sulphate, sodium sulphate and sodium chlorid in solutions of different strengths In twenty-four hours magnesium sulphate caused a slight inflammatory reaction, which in forty-eight hours, developed into a gangrene more diffuse than that produced by the sodium salts In all the numerous injections of magnesium sulphate which I have made in rabbits, guinea-pigs, and rats, no gross lesions were observed beyond occasional diffuse hemorrhages It often happened that as high as six subcutaneous injections of maximum doses of a 25 per cent solution were given during a single day without evidences of serious lesion or discomfort on the part of the animal <sup>28</sup>

What may possibly be a more serious complication is the probable action of magnesium salts on the kidneys Peck in 1913<sup>29</sup> in a study of the urine of cases of magnesium sulphate surgical anesthesia found hyaline casts in three out of five cases, which casts were not present before operation and disappeared after two days In one case the urine showed traces of albumin also Gates<sup>30</sup> tested this matter in experiments on dogs and found that sublethal doses of magnesium

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26 Wiesel Bericht uber Beobachteten Tetanusfalle, Off Proto d k k Gesell d Aerzte in Wien, Wien klin Wchnschr, Nov 27, 1914, No 49, p 1575

27 Reingruber Ueber die Behandlung des Tetanus mit subkutanen Injektionen von Magnesium-sulfuricum, Therap Monatsh, 1915, xxix, 148

28 Experiments are now being conducted in this laboratory on the local pathologic changes caused by subcutaneous and intramuscular injections of magnesium sulphate

29 Peck The Occurrence of Casts in the Urine Following Magnesium Sulphate Ether Anesthesia, Proc Soc for Exper Biol and Med, 1913-14, xi, 103-

30 Gates The Experimental Production of Hyaline Casts by Injections of Magnesium Salts, Proc Soc Exper Biol and Med, 1913-14, xi, 102

sulphate intramuscularly or intravenously would regularly produce the temporary appearance of hyaline casts in the urine. Neither epithelial or granular casts nor albuminuria were present. In Straub's<sup>15</sup> experiments the large amounts of sulphate solution thrown into the blood stream must have placed an enormous burden upon the kidneys. Careful records of excretion were preserved but there was no mention of casts or albuminuria, although it is not certain that examinations were made for these elements. The subject was deemed of sufficient importance to justify further experimentation, and in conjunction with Dr. Margaret Warwick investigations are being conducted on rabbits and other animals to determine the exact effects of the salt on the kidneys. Definite conclusions have not yet been reached, but some evidence has already accumulated which tends to indicate a slight toxic action on the renal epithelium. This is undoubtedly not of a severe enough grade to justify abandonment of the drug, but certainly continuous watch on the condition of the urine is indicated and in cases with an existing lesion of the kidneys considerable caution must be exercised in its use. The fact that the main, if not the sole, path of elimination is by way of the urine would alone justify such a warning.

There is no evidence that any organic changes are produced by the salt in other structures of the body, such as brain, spinal cord, nerves or heart muscle and, while no reported investigations have been made along these lines, we may safely assume that in therapeutic doses at least, these structures will not be seriously affected.

#### USE OF THE REMEDY IN THE PRESENT WAR

No review of this subject would be complete which does not mention the practical application of magnesium sulphate in tetanus seen during the present European war. Wars have always shown a high percentage of tetanus among the wounded and this conflict is no exception to the general rule.

Before prophylaxis was used routinely on all the fronts, many cases of tetanus developed, and while ideal therapeutic studies have been impossible because of the existing conditions, nevertheless there have appeared from time to time many interesting reports which deserve brief consideration. Because of the apparently greater incidence of tetanus in the early part of the war among German soldiers many of these reports have appeared in the German literature. As would be expected, exceedingly variable opinions are expressed. The group of physicians arrayed *against* the use of magnesium in tetanus is an imposing one. It includes such men as Czerny,<sup>31</sup> who, admitting the quieting and pain-diminishing effects, was not convinced it had

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31 Czerny. Einleitung in die Kriegschirurgie, Deutsch med. Wchnschr., 1914, No. 40, p. 1806.

any real value Angerer,<sup>32</sup> who early abandoned its use, Kreuter,<sup>33</sup> who had lost two cases in spite of the salt, Hochhaus,<sup>34</sup> whose not overenthusiastic comment classes magnesium sulphate as *ein recht brauchbares Mittel*, Muller,<sup>35</sup> Hohmeier,<sup>36</sup> and Goldscheider,<sup>37</sup> all of whom experienced "no certain success" or "no good success," Madelung,<sup>38</sup> who reserves final judgment, and Matthes,<sup>39</sup> who believes its good influence is limited to the first injection

Other workers are not so pessimistic and some frankly praise the beneficial effects of magnesium. Thus, Eunike<sup>40</sup> tried intralumbar injections up to 10 c c of a 10 per cent solution in eight very severe cases. Four patients recovered, in two the injections having a surprisingly good effect. He states that all complained of a constricted feeling in the lower part of the chest and heart region following the injection, and some suffered from illusions of hearing and hallucinations, which were relieved by morphin. He thinks the magnesium therapy is the best symptomatic method of treatment yet devised. Wiesel<sup>41</sup> studied 12 cases in Eiselberg's clinic in Vienna, using the salt subcutaneously up to 80 c c of a 25 per cent solution in one day and concluded that the combination of magnesium sulphate and chloral gave the best effect of all the narcotics.

Usener,<sup>41</sup> an enthusiastic advocate, used for a patient who was severely affected but who recovered, over 40 subcutaneous injections at intervals of two to four hours. He found 50 per cent solutions the least painful. No dangerous symptoms appeared. Dreyfus and Unger<sup>42</sup> treated 32 patients with 22 recoveries (mortality 31 per cent). They attribute their success to large doses of antitoxin and a definite narcosis therapy. This latter consisted of morphin, "luminal" or scopolamin

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32 Angerer, A. Behandlung des Wundstarrkrampfes, Munchen med Wchnschr, 1914, No 45, p 2226

33 Kreuter. Ueber einige praktische wichtige Gesichtspunkte in der Tetanusfrage, Munchen med Wchnschr, 1914, No 40, p 2045

34 Hochhaus. Erfahrung uber die Behandlung des Tetanus, Munchen med Wchnschr, 1914, No 46, 2253

35 Muller. Einige Ratschlage fur die Behandlung des Wundstarrkrampfes, Munchen med Wchnschr, 1914, No 15, p 2257

36 Hohmeier. Ueber Behandlung des Tetanus, Munchen med Wchnschr, 1915, No 5, p 160

37 Goldscheider. Klinische Beobachtungen uber Tetanus im Felde, Berl klin Wchnschr, 1915, No 10, p 229, and No 11, p 268

38 Madelung. Ueber Tetanus bei Kriegsverwundeten, Munchen med Wchnschr, 1914, No 52, p 2441

39 Matthes. Munchen med Wchnschr, 1915, No 5, p 160

40 Eunike. Zur Tetanusbehandlung mit Magnesiumsulfat, Munchen med. Wchnschr, 1914, No 45, p 2225

41 Usener. Indikation fur die subkutane Magnesiumsulfatbehandlung des Tetanus traumaticus, Munchen med Wchnschr, 1914, No 48, p 2323

42 Dreyfus and Unger. Die kombinierte Antitoxinuberschwemmungs- und Narkosetherapie des Tetanus, Munchen med Wchnschr, 1914, No 51, p 2417



(0.0005 gm) combined with intramuscular injections of magnesium sulphate. They first gave 20 gm and over per diem but found these were dangerous given intramuscularly and that 20 cc of a 25 per cent solution three times a day were sufficient to control paroxysms. In occasional very severe cases 8 to 10 cc of a 15 per cent solution were injected into the spinal canal. Wiener<sup>43</sup> obtained good therapeutic effects by subcutaneous injections of 10 cc of a 40 per cent solution. Of 40 patients treated only 16 died (40 per cent mortality). Finally from an experience with 25 cases Grundmann<sup>44</sup> states that magnesium sulphate surpasses all other narcotics in the treatment of this disease.

Reports from the other warring nations are comparatively few in number and meager in details. Feinmann<sup>45</sup> collected 95 cases of tetanus among 66,110 wounded Russians in the hospitals of Dvinsk. Of these 74 patients died (78 per cent). He saw no good results following the use of either serum or magnesium salts. Derujinsky<sup>46</sup> on the other hand, reports recovery in five out of six cases of tetanus treated with magnesium sulphate. In France Monod<sup>47</sup> reports using for tetanus cases heavy doses of chloral and intraspinal injections of magnesium sulphate with remarkable effects. Schoute<sup>48</sup> saw two recoveries in three cases of tetanus among Belgian soldiers treated with magnesium sulphate by intralumbar injections.

Somewhat more complete is the review of tetanus for the first year of the war in the military hospitals of England, which is given by Sir David Bruce<sup>49</sup> in the *Lancet*. He found records of 231 cases which showed a group mortality of 57.7 per cent as compared with a mortality of 78.2 per cent for 179 cases among British soldiers treated in France. Among these, few received treatment with magnesium sulphate. Two patients (Table 2, No. 29) were given 2 cc of a 25 per cent solution intraspinally. In the case of one of these the dose was repeated twice with recovery. Two other patients received similar treatment, one of them 7 cc of a 25 per cent solution. In another case one dose (amount not given) was injected subcutaneously. In

43 Wiener. Zur Therapie des Tetanus, *Deutsch med Wchnschr*, 1915, No. 4, p. 107.

44 Grundmann. Meine Beobachtungen über Tetanus im Frieden und im Felde, *Berl klin Wchnschr*, 1915, No. 8, p. 180.

45 Feinmann. Symptoms and Treatment of Tetanus, *Russk Vrach*, 1915, xiv, No. 39, p. 931.

46 Derujinsky. Recovery in Five Out of Six Cases of Tetanus Under Magnesium Sulphate, *Russk Vrach*, 1915, xiv, No. 14, rev in *Jour Am Med Assn*, 1915, lv, 1067.

47 Monod. *Acad de med*, Paris, 1915.

48 Schoute. Behandling van Tetanus traumaticus met inspuitingen van magnesiumsulfat, *Wederl Tijdschr v Geneesk*, 1914, ii, 1839.

49 Bruce. An Analysis of Cases of Tetanus Treated in Home Military Hospitals, *Lancet*, London, 1915, ii, 901.

other cases it was given by the mouth and rectum. These details are important as they show how unfair it would be to base judgments on the effect of a drug which was employed with so little recognition of the principles governing its proper use. Of the nine patients treated seven died. The author concludes "that this method of treatment is powerful and not without danger so that great caution ought to be used in its exhibition."

It seems particularly fitting to close this review with a brief reference to the latest "magnesium" article by Meltzer,<sup>50</sup> printed in both the *Berliner klinische Wochenschrift* and the *Lancet*. He first emphasizes the possibility that the cause of death in tetanus may be a direct result of the severe and exhausting spasms and that, by controlling these with magnesium sulphate, the life of the patient is lengthened and thereby his chances of recovery are increased, because of the formation within the body of antitoxin and the ability of the affected nerve cells to return to a normal state. He believes that magnesium narcosis is due to the passing of the magnesium sulphate out of the lymph stream into the free space which contains the points of contact of the branches of two or more neuron systems,<sup>51</sup> where the salt interrupts the conductivity of afferent and efferent impulses through the neurons. Thence arises the narcosis, the analgesia, and the relaxation of muscles. In discussing the various modes of administration, attention is again directed to the following points. The dosage by the intraspinal route should be 1 c c of a 25 per cent solution for every 10 kg (22 pounds) body weight; the effect of a 25 per cent solution, which is nearly molecular, is sharper and more certain than that of less concentrated solutions and that there is no clear evidence in the literature showing any toxic action of such injections on the heart, in cases of respiratory disturbance (which in his experience are very infrequent) one needs only to wash out the spinal canal with physiological saline, remembering that calcium chlorid, physostigmin or eserine do not afford relief in this particular method, and, finally in children Kocher's failure with the intraspinal method and Falk's success with the subcutaneous are perhaps due to the more rapid diffusion in the subdural and arachnoidal spaces of brain and cord in children, compared with adults, as well as the more rapid absorption of the salt from the subcutaneous tissues of the former.

The subcutaneous method gives a slower and hence a possible cumulative action, so that small doses frequently repeated are sufficient in many cases to produce a continuous effect. He emphasizes the sharp

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50 Meltzer. Magnesiumsulfat bei Tetanus, Berl klin Wchnschr, 1915, No 11, p 261. Use of Magnesium Sulphate in Treatment of Tetanus, Lancet, London, 1915, 1, 4791.

51 This space has been designated by Sherrington the synaptic membrane.

distinction to be made between subcutaneous and intramuscular injections, the latter acting in a much more rapid and hence more toxic manner. Therefore, caution is to be used not to penetrate accidentally too deeply with the injecting needle. The fact is reiterated that magnesium salts energize the anesthetic properties of ether so that a combination of the two in small doses leads to a deep narcosis and relaxation which is of considerable duration. Chloroform and other narcotics do not possess this property to nearly so marked a degree. He states that nephritis contraindicates the method for (at least) surgical anesthesia. Meltzer notes that a signal advantage of the subcutaneous method is the ease of controlling any dangerous effects of the drug. The administration of 1 mg of physostigmin or eserine (0.0015 gm.), the injection of an isotonic solution (about 2 per cent) of calcium chlorid into the muscles in doses of about 50 cc or into the veins of a 2 per cent solution in physiological saline up to 500 cc, being sufficient to remove at once the depressive action of the magnesium salt.

Lastly, in the routine treatment of tetanus Meltzer recommends starting with a subcutaneous injection of 0.3 gm or 12 cc of a 25 per cent solution per kilo (about 10 cc for a normal male adult) repeated four times a day. If severe spasms occur, ether should be used and the dose of magnesium increased to 0.5 gm per kilo (16 cc of 25 per cent solution for adult male). The bladder may need to be emptied by catheterization. In case of danger from respiratory failure one can resort to the remedies mentioned above as well as the application of an Esnarch bandage to hinder absorption of the salt. In desperate cases artificial respiration should be used. If the symptoms are too severe or the subcutaneous injections fail, the intraspinal method is advised. Antitetanus serum should always be used.

To this admirable summary of this subject by Meltzer there is little to add in conclusion. There can be no doubt in the minds of those who review the evidence that in magnesium sulphate we possess a most valuable addition to our armamentarium in the treatment of tetanus. No such imposing array of facts can be brought forward in favor of chloral or allied narcotic agents, even granting their occasionally apparent good effects.

One further point needs emphasis. It is clearly evident that the drug must be used boldly, if its maximum therapeutic effect is obtained, that this bold use is subject to certain dangers, undoubtedly greater in some patients than in others, that these dangers, when threatening, may be rapidly relieved by simple and easily applied measures, and that, therefore, while this salt is being used, the patient must be under continuous expert attendance, with preparations already made to administer, rapidly, restorative remedies. In my studies of the treatment of tetanus both in man and in animals I have been struck by the need of

constantly watching the patient's condition. The disease at its best is a most desperate one and our remedies must be used as soon as possible and their therapeutic limits attained at the earliest possible moment. It is only in this way that good results may be expected in severe cases. We watch a patient under anesthesia, a woman in childbirth, a case threatened with internal hemorrhage. How much more important in tetanus, with almost sure death before us, that we employ our resources to the limit and immediately meet every change with the necessary maximum therapeutic measure!

The treatment of tetanus has not yet reached the ideal stage. Prophylaxis of all dirty wounds is still our surest weapon of defense. However, it is difficult to avoid the conclusion that in outbroken cases, in addition to antitoxic serum, one's duty is sadly neglected if early, vigorous, and continuous efforts are not made to control the spasms, relieve the distress and pain, and give rest and nourishment by subcutaneous injections of magnesium sulphate in amounts large enough and given often enough to bring about the desired results.

have adopted the following standards with which to compare the metabolism of my fat subjects

Age, Years	Male	Female
13	46	
15	43.5	
20-30	39.0	37.0
30-40	38.0	36.0
40-50	36.0	34.0
50-60	35.0	33.0

These standards while to a certain extent arbitrary, are, I believe, fairly near the real average. In choosing them I used DuBois' age

TABLE 1—METABOLISM DATA—

Subject	Date	Age	Weight Kg	Height, Cm	Surface Area Square Meters (Linear Formula)	Per centage "Over" weight	CO <sub>2</sub> per Minute, cc*	O <sub>2</sub> per Minute, cc*
Mrs L. I	8/ 4/15	56	145.3	163.5	2.79	105	227	324
	10/ 6/15		144.5		2.78†		220	343
	10/11/15		141.5		2.75†		226	326
	10/16/15		139.0		2.73†		219	301.5
	10/17/15		139.0		2.73†		209	314
	10/18/15		138.0		2.72†		203	305
	10/20/15		137.5		2.71†		205	309
	11/13/15		133.8		2.68†		217.5	298.5
	11/20/15		132.0		2.66†	90	213	294
Subject's aver								
Mrs McI	1/ 7/16	46	127.0	157.5	2.29	95	203	299
Mrs Shn	11/ 4/15	30	113.0	155	2.21	80	184	283
	11/14/15		107.5		2.15†		190	249
	11/26/15		106.5		2.14†		195	254
	12/17/15		102.0		2.10†	60	168	250
Subject's aver								
Miss P. M	11/ 1/15		99	172	2.11	45	209	245
Mr Z	12/ 1/15	30	93	167.5	1.99	50	272	278
H S (boy)	9/ 2/15	13	57.6	146.5	1.47	50	189	236
Mr P. A. M	10/13/15	24	95	172.5	2.13	40	253	317
Mr Oh	9/16/15	54	102	178.5	2.145	30		282

\* The figures for CO<sub>2</sub> and O<sub>2</sub> are in all cases the average of three consecutive ten minute periods on the Benedict apparatus

† Corrected from original determination on basis of 0.01 sq m per kg

curve, assuming that changes in the metabolism due to age, expressed in terms of Meeh's area, would run parallel with those expressed in terms of the linear formula area

The clinical data on the new subjects are as follows

CASE 1—Mrs L L, aged 36 Has had pneumonia twice Five pregnancies, four of them ending in miscarriage Positive Wassermann now Left ovary removed eight years ago, since then there have been neither pregnancies nor catamenia Her attitude toward sexual matters is normal She is nearly always thirsty and has a definite polyuria Some dyspnea on exertion Her appetite, she says, is very good She leads a sedentary life Has always been fat At 15 years she weighed 190 pounds, at 20, 200 pounds, at 35, 375 pounds Physical Examination Enormous obesity, slightly irregular pupils, knee jerks

ON ALL NEW SUBJECTS

R Q :	Pulse	Calories per Sq M and Hour (Linear Formula)	Calories per Kg and 24 Hrs	Total Calories per 24 Hours (Basal)	Standard Basal Metabolism for Age and Sex Calories per Sq M and Hour	Percentage Deviation from Standard	Remarks
0 70	79	32 6	15 0	2,185	36	— 9 4	
0 69	71	34 7	16 0	2,315		— 3 6	
0 69	73	33 3	15 5	2,200		— 7 5	
0 70	66	31 0	14 6	2,035		—13 9	Started a complete fast today
0 67	70	32 3	15 2	2,120		—10 3§	Second day of complete fast
0 67	70	31 5	14 9	2,060		—12 5§	Third day of complete fast
0 66	73	32 0	15 2	2,035		—11 1§	
0 73	68	31 5	15 2	2,030		—12 5§	Has been on thyroid extract for last 5 days Started at 3 grains and increased gradually to 12 grains per day
0 72	67	31 1	15 1	1,990		—13 6§	Has been on pituitary substance (B W & O) for last 5 days
0 69		32 7	15 3			— 9 2	Started at 8 grains and increased to 24 grains per day
0 68	65	36 7	15 9	2,020	34	+ 7 9	
0 65	68	36 1	16 0	1,910	36 5	— 1 1	
0 76	68	33 0	15 8	1,705		— 9 6	
0 77	68	33 9	16 3	1,740		— 7 1§	Has been on thyroid extract for last 5 days Started at 1½ grain per day and increased up to 7½ grains per day
0 67	66	33 5	16 4	1,685		— 8 2§	No food for 48 hours Has been on ovarian extract (Armour) for last 5 days Started at 2 grains, worked up to 16 grains per day
0 705		34 5	16 3			— 5 5	
0 85	65	33 9	17 3	1,715	37	— 8 4	
0 98		40 7	20 5	2,010	38 5	+ 5 7	
0 80		46 2	28 3	1,630	46	+ 0 8	
0 80		42 9	23 1	2,190	39	+10	
		37 9	19 1	1,950	35	+ 8 3	

‡ It will be noted that in the case of Mrs L L, Mrs I and Mrs Sha the R Q is very low This, undoubtedly due to the fact that these patients were on a very low carbohydrate intake  
§ Not included in averages

absent, and a large ventral hernia, otherwise negative. Blood, urine, pulse and blood pressure normal. Sugar tolerance: no reduction after 150 gm levulose, very slight reduction after 200 gm of levulose. Roentgen-ray Examination: Sella turcica normal.

CASE 2—Mrs. McI., aged 46. Nothing remarkable about history or physical examination. Normal save for obesity. Had always been stout. Weighed 250 pounds when she was 16 years old. She has always been a heavy eater and is particularly fond of sweets. Has led a sedentary life. At the present time she is passing through the menopause.

CASE 3—Mrs. Sha., aged 30. Has had two miscarriages and five pelvic operations. The last operation five years ago, at which time all the pelvic organs were removed, there have been no catamenia since. Before that she had been quite thin but following this last operation gained weight rapidly and steadily to the present time. She says that she is not a heavy eater. Leads a fairly active life. Physical Examination: Negative save for obesity. Sugar tolerance: sugar appeared after 150 gm of levulose.

CASE 4—Miss P. M. Has been stout since the age of 15, at which time she had a "goiter" without symptoms of hyperthyroidism, neck at that time measured 16 inches. Following this, had some sort of medication by mouth for two years and neck went down to 14 inches. Eats very little, and leads a very active life, yet gains weight steadily. Catamenia started at 13 and have always been regular. Skin is rather dry, but she perspires normally, hair has been falling and getting brittle. Does not feel the cold particularly and is neither nervous nor abnormally placid. Physical Examination: Unimportant except for the obesity.

CASE 5—Mr. Z. Perfectly healthy medical student of 30, has been gaining weight for the last five years. Says he does not overeat.

CASE 6—H. S., boy, aged 13. Always has been very fat, as have all his family. Has been well save for numerous upper respiratory tract infections. Eats large quantities of carbohydrate food, and eats continually between meals. Physical Examination: Shows marked obesity, small genitalia (though patient says erection and ejaculation occur), female type of breast, no pubic or axillary hair. Eye grounds and visual fields normal. Roentgen-ray Examination: Sella turcica normal.

CASE 7—Mr. P. A. M., a normal man of 24. Has been stout since boyhood. Is a fairly heavy eater and takes little exercise.

CASE 8—Mr. Ch., man of 54. Has been very stout for years, more so five years ago than at present. History and physical examination not remarkable. When first seen had a slight glucosuria which cleared up readily on slight restriction in carbohydrates.

The experimental data on the new subjects are all given in Table 1.

In Table 2 the subjects previously reported are compared with the new standards so that they may be used in the discussion of the whole series.

#### DISCUSSION OF RESULTS

The basal metabolism of each subject has been compared with an appropriate standard for his or her age and sex, and the percentage variation from that standard noted. Table 3 shows the average metabolism of all the subjects in Tables 1 and 2 divided into two groups, one group including the subjects less than 60 per cent over-

weight, and the other the subjects more than 60 per cent overweight. In the former group the actual metabolism is only 0.3 per cent below the average of the standards for the same subjects, and in the latter group the actual is 2.3 per cent below the standard average.

Taking the series as a whole, then, we may certainly say that there is no characteristic change whatsoever in the basal metabolism even in very extreme cases of obesity. Or, to put it more concisely, extreme obesity may occur in persons with a normal heat production per unit of surface area.

TABLE 2—DATA ON CASES PREVIOUSLY REPORTED

Subject	Age	Weight, Kg	Height, Cm	Surface Area Square Meters (Linear Formula)	Per centage Overweight	R Q	Calories per Sq M and Hour	Calories per Kg and 24 Hours	Standard Basal Metabolism for Age and Sex Calories per Sq M and Hour	Percentage Deviation from Standard
Mrs B	44	179.0	163.0	2.95	160	0.78	35.4	14.0	34	+4.1
Mrs McK	48	103.0	144.5*	1.86§	120	0.75	34.8	15.0	34	+2.3
N K ♂	16	94.0	165.0	2.11†	55	0.76	36.4*	19.6	43.5	-16.3
Mrs M	28	87.0	161.0	2.01	30	0.75	31.1	17.2	36	-13.6

\* Values corrected since appearance of first paper as explained in text.

† Obtained from area of Mrs M, a subject of nearly same weight and height, by equation, Area by Meeh of A = Area of A by linear formula = Area by Meeh of B = Area of B by linear formula.

§ This area was obtained by direct measurement of casts of the body as described in DuBois' paper on body surface determination (Note 5). It was for a weight of 93 kg. For 103 kg, 1.96 would be more nearly correct. However, the conclusions regarding the normality of the metabolism would hold in either event.

TABLE 3—AVERAGE METABOLISM OF ALL CASES IN TABLES 1 AND 2

Group	Number of Subjects	Calories per Sq M and Hour, as Determined Group Average	Calories per Sq M and Hour Average of "Standards" of Individual Members of Group	Variation of Group Average Metabolism Observed, from "Standard" Average
Subjects more than 60% overweight	5	34.8	34.9	-0.3%
Subjects between 30% and 60% overweight	7	38.4	39.3	-2.3%

So much in regard to the series as a whole. Individually we can pick several cases that seem to have an abnormal metabolism. Following the Sage Institute investigators I shall consider a metabolism more than 10 per cent from its appropriate standard as of questionable normality. On looking over the series we find that N K and Mrs M (Table 2) both have a metabolism more than 10 per cent below the normal. Reference to the clinical histories of these cases will show



that they both presented some evidence of hypopituitarism H S (Table 1), however, who likewise was thought to be hypopituitary, had a normal metabolism Mrs L L, whose metabolism was sometimes below 10 per cent, also presented some evidence of hypopituitarism in that her sugar tolerance was increased From all of this we may say that out of a series of twelve obese subjects three showed a slight reduction in basal metabolism, and that all of these three showed some clinical evidence of disturbed internal secretion

#### CONCLUSIONS

1 The majority of obese subjects show no alteration in the basal metabolism, as expressed in terms of their surface area, even though the obesity is of a most extreme type

2 Occasionally a slight reduction occurs and in such cases clinical evidence of disturbed internal secretion is present

My sincere thanks are due to Dr D L Edsall, Dr E F DuBois and Dr F G Benedict, all of whom were good enough to read the original manuscript and make many valuable suggestions and criticisms

15 Chestnut Street

#### CORRECTION

In the article by Drs I H Levy and J L Kantor, entitled "A Clinical Study of Delayed Gastric Emptying," *THE ARCHIVES OF INTERNAL MEDICINE*, April, 1916, p 476, in the section on Tone of Stomach, p 479, the second sentence should read "This so-called peristolic function of Stiller is impaired in muscular weakness (atony or myasthenia gastrica)

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## A STUDY OF SALT, NITROGEN AND WATER EXCRETION IN NEPHRITIS \*

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### INTRODUCTION

It has been known for a long time that in cases of chronic nephritis there is a disturbance in salt and nitrogen elimination. A number of observers have called attention to the fact that frequently the excretion of salt is disturbed proportionately more than that of nitrogen while occasionally the reverse is true. Several methods of studying these factors have been suggested.

Von Monakow<sup>1</sup> placed patients on a standard diet containing each day approximately the same amounts of salt, nitrogen and water, to which were added on different days a definite amount of salt (10 gm of sodium chlorid) or nitrogen (20 gm of urea), the daily excretion of salt, nitrogen and water was quantitated and the effects of the added salt and nitrogen were noted by comparing the excretion after these were given with the previous daily excretion. This method we will speak of as the "added urea and salt test."

Hedinger and Schlager<sup>2</sup> gave on a single day to patients a diet composed of several meals containing varying amounts of the natural diuretics, water, salt, xanthin bases and caffeine and collected the urine in two-hour portions throughout the day. In these portions the amounts of fluid and salt, and the specific gravity and percentage of salt were determined. For several days prior to this day the patients were on a diet containing daily approximately the same amounts of fluid, salt and protein. Hedinger and Schlager did not quantitate the nitrogen output, but we have done so in making the test. This test we term for brevity "the two-hour renal test."

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\* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston

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1 Von Monakow *Deutsch Arch f klin Med*, 1911, cxi, 248

2 Hedinger and Schlager *Deutsch Arch f klin Med*, 1914, cxiv, 120

Ambard and his associates<sup>3</sup> have investigated the relation between urea nitrogen and salt in the blood and urine and by means of formulas have expressed this relation as an index of excretion. More recently McLean<sup>4</sup> has modified and amplified these formulas of Ambard.

At the Peter Bent Brigham Hospital under the direction of Dr. Henry A. Christian I have been studying the water, salt and nitrogen elimination in chronic nephritis by one or all of these methods with the view to utilizing them as measures of the functional power of the kidney. In addition other tests of renal function have been carried out in the study of these same patients. With this data it seems worthwhile to report the results obtained and to discuss the relative value of some of these tests.

#### METHODS

The "added urea and salt test" has been carried out much as described by von Monakow. Our patients have been placed on a diet containing 75 gm. of protein, 4 gm. of sodium chloride and 1,500 cc. of water with a caloric value of 2,000 to 2,200.<sup>5</sup> After the output of fluid, salt and nitrogen reaches an equilibrium on this diet, on one day 10 gm. of additional salt is given, and several days later the patient receives 20 gm. of urea. This order may be reversed. The daily output of urine, salt and nitrogen is determined<sup>6</sup> and charted as shown in Figure 1.

After salt or nitrogen are added to the diet in normal individuals their excretion after forty-eight hours returns to its previous level. In the diseased kidney this may not be the case. Sometimes the added salt or urea produces a diuresis and this disturbs the elimination of both salt and nitrogen, the increased water output carrying out with it more

3 Ambard. *Physiologie normale et pathologique des reins*, Paris, 1914.

4 McLean. *Jour. Exper. Med.*, 1915, **xvii**, 212.

5 Of course it is to be remembered that these values are only approximate. In the first place patients who are very sick cannot eat regularly from day to day the total food given, and daily variations arise in this way. In the second place the values as given are calculated from tables of food values and do not represent actual values determined by analyses of samples of the various meals. There must be a considerable difference between the average values stated for a given food product and the actual amount contained in a single sample of that food. Hence it is to be clearly recognized that this method of renal testing as well as the others involving calculated diets, as carried out by us is in no sense an exact metabolic study, and variations between calculated intake and observed output are necessarily frequent. The weighing of food prepared for the patients and the subtraction of food not eaten has been done with care, and precautions have been taken to insure accurate urine collections. Errors in this part of the work have been reduced to small figures and where evident mistakes occurred in these parts of the work the results have been discarded.

6 In making the nitrogen and salt determinations I acknowledge the assistance of a chemical technician whose salary was paid from a fund given to the Medical Service of the Peter Bent Brigham Hospital by Dr. F. C. Shattuck.

salt or nitrogen. Consequently it is desirable to observe the effect of each added substance for several days after it is given before introducing the other. Then it often takes several days on the diet before salt, nitrogen and water excretion reach an approximately constant rate of excretion. These several factors render it desirable to prolong the added urea and salt test over a period of ten or twelve days, and in some cases even longer.

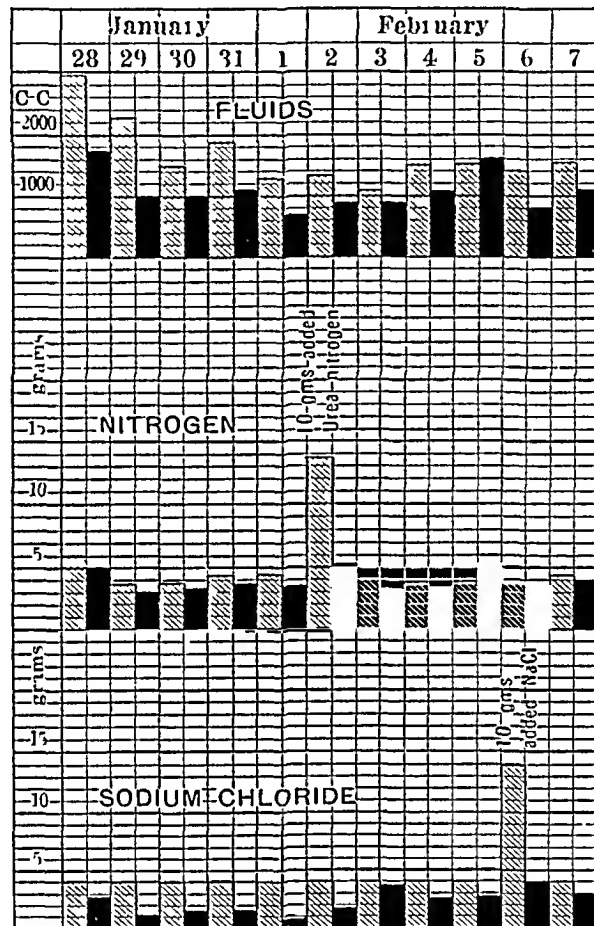


Fig 1, Case XVI—The hatched columns indicate intake, the cross-hatched columns output. The upper series are for fluids, the middle for nitrogen and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

The added urea and salt test gives us rather early evidence of disturbed nitrogen and salt elimination of the kidney, as shown by delayed and deficient excretion of these substances. Simple, logical and direct as it seems, the test has many practical difficulties. In the ten or twelve days needed to carry it out the patient may tire of the hospital and refuse to stay, changes in the patient's condition may necessitate a change in diet or other interference with the conditions under which the experiment is being carried out, a woman may begin to menstruate; portions of the urine may be lost unavoidably as when the patient voids

at stool, etc., or the diet may become very monotonous. Sometimes, especially during the formation of edema, there may be a storing up of nitrogen or salt with a subsequent discharge of the same either just before or coincidently with the giving of the added urea or salt. This, of course, interferes with the correct interpretation of the changes in the excretion curves. Urea taken by mouth sometimes causes a diarrhea, with consequent probable loss of an unknown amount of nitrogen in the feces. This would have the effect of showing an apparently lower nitrogen excretion than the kidneys are really capable of handling. Of course variations in rate and completeness of absorption from the gastro-intestinal tract introduce possible errors in such dietary tests. Tissue retention, especially of salt, is another possible source of error in any such test.

On account of these various difficulties with the added urea and salt test some other form of test seemed desirable which would shorten the period of observation and reduce the probability of the difficulties enumerated above. The Hedinger and Schlager "two-hour renal test" can be completed, as far as the patient is concerned, in twenty-four hours. In this respect, therefore, it would seem to have a decided advantage over the previous test, as by shortening the time the probability of the disadvantages enumerated above is much reduced. To compare the two tests both were carried out on a number of patients.

In using the two-hour renal test the diet has been slightly changed from that described by Hedinger and Schlager, so that we gave the following menu for the several meals.

Seven a. m., coffee, milk, sugar, toast and butter, 10 a. m., milk, toast and butter, 12 30 p. m., bouillon, broiled steak, butter, mashed potato, butter, toast and butter, coffee, milk and sugar, 4 p. m., tea, milk, sugar, crackers, 7 p. m., soft egg, blanc mange (one egg, sugar, corn starch, milk), and cream. Amounts sufficient to give approximately 2,500 calories, 1,550 cc of fluid, 76 gm of protein, 127 gm of fat, 245 gm of carbohydrates and 58 gm of sodium chlorid.

On the two days preceding the test day the patient usually had a diet containing 2,000 calories, 75 gm of protein and 4 gm of sodium chlorid. The test diet is a mixed diet containing known amounts of water, nitrogen and chlorid together with food diuretics of various types (purins, salt, water, etc.). As can be seen, the diet is divided into five unequal portions given at definite times during the day. Each portion contains known but varying amounts of fluid, nitrogen and salt. The noon meal particularly contains large amounts of the above elements.

Two-hour specimens are collected from 7 a. m. to 9 p. m. and one "night specimen" is obtained containing all the urine passed between 9 p. m. and 7 a. m. Each specimen is analyzed for volume, specific

gravity, total nitrogen, nitrogen concentration, total chlorid, and chlorid concentration, and the results are charted as in Figure 2

The purpose of the test is to find out to what extent and in what manner the diseased kidney, under stimulation by the different diuretics taken in the food, reacts in putting out the varying amounts of water, nitrogen, and chlorid ingested Hedinger and Schlayer have shown that normal cases respond by putting out water and salt promptly and

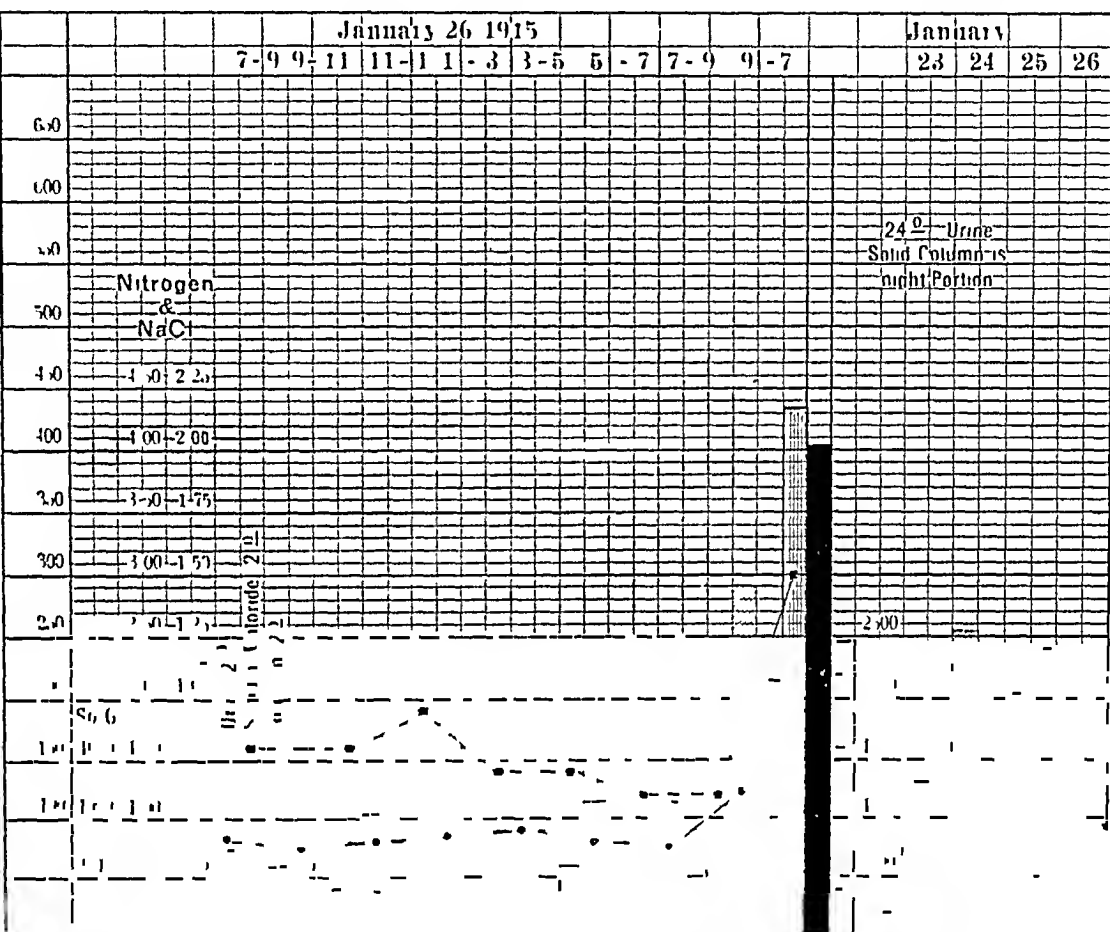


Fig 2, Case XVI—The series of columns beginning at the left give the amount of urine, sodium chlorid, and nitrogen in each two-hour portion from 7 a m to 9 p m and in the portion from 9 p m to 7 a m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

in good amounts. The diseased kidney, however, may show that its power to excrete these elements is fixed at a certain level and that this level is too low to accommodate the large amounts of these elements ingested, especially at the noon meal. These "fixed" cases show a curve of excretion that approaches more or less a straight line. Instead of getting the normal "picket fence" curves, we find some or all of the curves of excretion more or less flattened out.

## CASES

In our work this year we have applied these tests to thirty cases of chronic nephritis of varying degrees of severity, some of them complicated by cardiac conditions. In one case the test was performed three times. Other tests of renal function have been made and all patients have been studied carefully to determine, in so far as is possible, their general condition. A brief summary of the records of these patients follows. In each case the "added salt and urea" and the "two-hour renal" tests are recorded in the form of charts of the type shown in Figures 1 and 2 of this paper and in Chart I to XII of a previous paper<sup>7</sup> because in this graphic way the renal function is shown most clearly. Owing to the expense of reproduction the charts in each case reported are replaced by tables, but in the discussion following the summary of the cases the findings are described in terms of curves as shown in the charts. Cases 1 to 4 show no renal lesion and are included for comparison. Cases 5 to 34 show various types of chronic nephritis with or without cardiac involvement.

CASE 1—No 1662 male 14, student. Diagnosis: Rheumatic fever, chronic cardiac valvular disease, aortic and mitral regurgitation. Urine: Acid, specific gravity, 1.019-1.040; albumin, none to very slight trace; no sugar. Sediment: Very rare hyaline cast with fat and cells adherent. Blood Pressure: 114-130 systolic, 46-60 diastolic.

TABLE 1—TWO-HOUR RENAL TEST

November 4	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 a m	252	1.014	1.51	0.60
9 11 a m	362	1.009	1.05	0.29
11 a m 1 p m	95	1.017	0.35	0.37
1-3 p m	69	1.028	0.19	0.28
3-5 p m	96	1.026	0.33	0.34
5-7 p m	84	1.026	0.19	0.23
7-9 p m	57	1.029	0.21	0.36
9 p m 7 a m	153	1.027		

Summary—Water: No fixation. Slight but somewhat delayed response to noon meal. Chlorid: No fixation. Slight but delayed response to noon meal.

<sup>7</sup> Christian, Frothingham, O'Hare and Woods: Studies of Nephritis, *Am Jour Med Sc*, 1915, cl, 655.

CASE 2—No 1755, male, aged 25, single, shoe cutter Diagnosis Pleurisy with effusion, tuberculosis of pleura Urine Acid, specific gravity, 1.010-1.029, albumin, none to the slightest possible trace, no sugar Sediment No casts Blood Pressure 130 systolic, 76 diastolic

TABLE 2—Two-Hour Renal Test

November 29	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 9 a m	195	1.016	1.44	0.74
9 - 11 a m	133	1.022	1.30	0.98
11 a m - 1 p m	333	1.012	1.17	0.35
1 3 p m	251	1.015	1.68	0.67
3 5 p m	121	1.023	1.19	0.98
5 - 7 p m	126	1.019	0.79	0.63
7 9 p m	281	1.012	0.56	0.20
9 p m - 7 a m	106	1.019	1.71	0.42

Summary—Water No fixation Good and prompt response to noon meal  
 Chlorid No fixation Good and prompt response to noon meal

CASE 3—No 1822, male, aged 21, single, car cleaner Diagnosis Hyperchlorhydria Urine Acid, specific gravity, 1.019-1.023, albumin, none to slightest trace, no sugar Sediment No casts Blood Pressure 124 systolic, 90 diastolic

TABLE 3—Two-Hour Renal Test

November 6	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 9 a m	157	1.021	1.55	0.99
9 11 a m	247	1.014	1.79	0.75
11 a m - 1 p m	310	1.011	1.40	0.45
1 3 p m	192	1.012	0.84	0.43
3 5 p m	114	1.022	1.05	0.90
5 7 p m	174	1.022	1.60	0.93
7 9 p m	155	1.019	1.10	0.71
9 p m - 7 a m	168	1.016	0.78	0.46

Summary—Water No fixation of amount or specific gravity Good and prompt response to noon meal Salt No fixation of amount or concentration Good response, somewhat delayed, to noon meal



CASE 4—No 2656, female, aged 38, widow, domestic Diagnosis Syphilis, pulmonary tuberculosis (?) Urine Acid, specific gravity, 1006-1018, albumin, none to slight trace, no sugar Sediment No casts Blood Pressure 106 systolic, 72 diastolic

TABLE 4—TWO-HOUR RENAL TEST

May 18	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	187	1 010	1 68	0 90	0 31	0 17
9-11 a m	119	1 015	0 47	0 35	0 60	0 50
11 a m 1 p m	118	1 014	0 30	0 25	0 43	0 36
1-3 p m	80	1 023	0 48	0 60	0 59	0 74
3-5 p m	160	1 023	0 96	0 60	1 18	0 74
5-7 p m	93	1 024	0 93	1 00	0 55	0 59
7-9 p m	115	1 023	1 10	0 95	0 82	0 71
9 p m 7 a m	295	1 025	2 36	0 80	1 03	0 68

Summary—No fixation Fairly good response to noon meal in all elements, slight delay in water and salt

CASE 5—No 1624, male, aged 31 single, junk dealer Diagnosis Chronic nephritis, parenchymatous Urine Acid, specific gravity, 1 020-1 032, albumin, 12 per cent to 2 per cent, no sugar Sediment Many granular and hyaline cases Blood Pressure 150-127 systolic, 110-78 diastolic

TABLE 5—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Nonprotein N <sub>2</sub> of Blood, Gm per Liter
September 11	28 0	0 40
September 16		0 231
November 6	47 5	
November 16	52 5	

TABLE 6—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
10/ 5	11 0	9 4	4 0	2 5	Poor response to both added urea and salt
10/ 6	11 0	5 2	4 0	1 5	
10/ 7	21 0	11 0	4 0	2 5	
10/ 8	11 0	7 5	4 0	1 6	
10/ 9	11 0	9 5	14 0	2 4	
10/10	11 0	8 8	4 0	3 6	

TABLE 7—Two-Hour Renal Test

November 14	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 - 9 a m	74	1 025	1 32	0 95
9 - 11 a m	82	1 023	0 42	0 25
11 a m - 1 p m	118	1 022	0 79	0 33
1 - 3 p m	98	1 026	0 62	0 32
3 - 5 p m	128	1 024	0 63	0 24
5 - 7 p m	130	1 022	0 99	0 39
7 - 9 p m	134	1 023	0 98	0 35
9 p m - 7 a m	284	1 025		

*Summary*—Water Fixation of specific gravity, none of volume Fair response in normal time to noon meal Chlorid Fixation of both amount and percentage concentration with the exception of the early morning specimen Fair response in normal time to noon meal

CASE 6—No 1683, male, aged 33, single, laborer Diagnosis Chronic nephritis, hypertension, chronic cardiac valvular disease, mitral stenosis, auricular fibrillation Urine Acid, specific gravity, 1 012-1 023, albumin, none to slightest possible trace, no sugar Sediment Rare hyaline cast Blood Pressure 188-160 systolic, 140-118 diastolic Phenolsulphonephthalein in two hours 43 per cent

TABLE 8—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
10/2	11 0	7 0	4 0	0 9	Abnormally good response to added urea, poor response to added salt
10/3	11 0	9 0	4 0	0 8	
10/4	21 0	15 0	4 0	1 6	
10/5	11 0	29 0	14 0	6 0	
10/6	11 0	15 0	4 0	4 5	
10/7	11 0	9 8	4 0	2 7	

TABLE 9—Two-Hour Renal Test

Nov 29, 1914	Water, cc	Specific Gravity	Salt	
			Grams	Per Cent
7-9 a m	54	1 027	0 022	0 04
9-11 a m	50	1 025	0 01	0 02
11 a m-1 p m	54	1 026	0 016	0 03
1-3 p m	51	1 028	0 015	0 03
3-5 p m	66	1 029	0 04	0 06
5-7 p m	69	1 028	0 06	0 09
7-9 p m	65	1 028	0 039	0 06
9 p m-7 a m	231	1 027	0 254	0 11

*Summary*—Fixation of water and specific gravity, the latter at a high level. Some fixation of concentration of salt, less of total output of salt.

CASE 7—No 1898, male, aged 57, married. Diagnosis: Chronic nephritis, hypertension, chronic myocarditis, auricular fibrillation. Urine: Acid, specific gravity, 1 010-1 023, albumin, very slight trace to slight trace, no sugar. Sediment: Occasional hyaline and granular cast. Blood Pressure: 190-170 systolic, 130-90 diastolic.

TABLE 10—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Urea N <sub>2</sub> of Blood, Gm per Liter
November 13	43 0	0 25
December 1	44 5	
December 15	35 0	
December 23		
December 27	38 5	

TABLE 11—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/20	11 2	8 0	2 9	4 4	Good response to added urea, poor response to added salt
12/21	11 2	7 1	2 9	2 2	
12/22	20 4	13 2	3 0	3 4	
12/23	10 6	16 4	2 9	1 5	
12/24	10 6	14 4	2 9	1 0	
12/25	11 4	23 0	13 8	3 4	
12/26	10 8	10 0	2 8	2 2	

TABLE 12—Two-Hour Renal Test

Nov 16, 1914	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 - 9 a m	138	1 015	0 50	0 35
9 - 11 a m	128	1 014	0 44	0 34
11 a m - 1 p m	119	1 015	0 44	0 37
1 - 3 p m	99	1 019	0 44	0 43
3 - 5 p m	110	1 019	0 58	0 52
5 - 7 p m	95	1 019	0 47	0 48
7 - 9 p m	84	1 020	0 34	0 38
9 p m - 7 a m	388	1 019	1 68	0 42

*Summary* — Water Some fixation of volume, none of specific gravity Slight, delayed response to noon meal Salt Amount fixed, percentage concentration not Slight, delayed response to noon meal

CASE 8—No 1918, male, aged 54 single, laborer Diagnosis Chronic nephritis and hypertension Urine Acid, specific gravity, 1 015-1 024, albumin, none to very slight trace, no sugar Sediment Rare granular cast Blood Pressure 254-200 systolic, 138-118 diastolic

TABLE 13—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Nonprotein N <sub>2</sub> of Blood, Gm per Liter
November 17	49 0	0 31
December 1	42 5	
December 2		0 39
December 8	49 0	0 25

TABLE 14—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
11/23	11 0	7 5	4 0	2 4	Good response to added urea, poor response to added salt
11/24	11 0	9 2	4 0	3 4	
11/25	21 0	12 0	4 0	2 4	
11/26	11 0	11 0	14 0	2 4	
11/27	11 0	9 0	4 0	5 0	

TABLE 15—Two-Hour Renal Test

December 2	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7-9 a m	132	1 015	0 37	0 28
9 11 a m	67	1 019	0 087	0 13
11 a m 1 p m	104	1 018	0 146	0 14
1 3 p m	111	1 021	0 144	0 13
3 5 p m	38	1 021	0 418	0 11
5 7 p m	122	1 022	0 146	0 12
7-9 p m	186	1 016	0 744	0 40
9 p m 7 a m	550	1 016	2 67	0 46

*Summary*—Water No fixation Fair but delayed response to noon meal  
 Chlorid Suggestion of fixation of both amount and percentage concentration  
 Slight, delayed response to noon meal

CASE 9—No 1946, male, aged 36, married, clerk Diagnosis Chronic nephritis, hypertension, arteriosclerosis Urine Acid, specific gravity, 1 013-1 025, albumin slight trace to large trace, no sugar Sediment Some hyaline and finely granular casts Blood Pressure 240-190 systolic, 205-140 diastolic

TABLE 16—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Nonprotein N <sub>2</sub> of Blood, Gm per Liter
November 25	49	0 28
December 8	48	

TABLE 17—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/ 5	11 0	8 0	4 0	2 4	Good response to added salt Apparently a fair response, at least to added urea
12/ 6	11 0	8 6	4 0	2 4	
12/ 7	21 0	10 0	4 0	2 6	
12/ 8	11 0	Lost	4 0	Lost	
12/ 9	11 0	9 4	4 0	3 0	
12/10	11 0	9 9	14 0	10 0	
12/11	11 0	7 8	4 0	2 8	

TABLE 18—Two-Hour Renal Test

November 29	Water, c c	Specific Gravity	Salt	
			Grams	Per Cent
7 9 a m	93	1 023	0 065	0 07
9 - 11 a m	49	1 026	0 054	0 11
11 a m 1 p m	78	1 025	0 624	0 03
1 - 3 p m	71	1 026	0 071	0 10
3 5 p m	71	1 025	0 085	0 12
5 - 7 p m	101	1 025	0 172	0 17
7 - 9 p m	58	1 026	0 064	0 11
9 p m - 7 a m	400	1 022	0 88	0 22

*Summary*—Water Volume and specific gravity fixed Slight, delayed response to noon meal Chlorid Percentage concentration fixed Amount fixed except in one period Good and prompt response to noon meal

CASE 10—No 2006, female, aged 45, widow, domestic Diagnosis Chronic nephritis, hypertension, chronic myocarditis, chronic cardiac valvular disease, mitral regurgitation Urine Acid, specific gravity, 1 009-1 013, albumin, slight trace to trace, no sugar Sediment Rare hyaline and granular casts Blood Pressure 210-160 systolic, 100-80 diastolic

TABLE 19—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours	Blood Urea N <sub>2</sub> , Gm per Liter	Nonprotein N <sub>2</sub> of Blood, Gm per Liter	Blood Chlorid,* Gm per Liter	Alveolar CO <sub>2</sub> , mm
12/11			0 80		
12/12		0 67	0 95	5 36	
12/17		0 63	0 91	5 68	
1/ 2	Slight trace				
1/ 7	None				
1/11					19 09
1/14					23 40
1/15	None				41 50
1/16					39 80
1/17					36 90
					25 10

\* Whole blood

TABLE 20—Two-Hour Renal Test

December 17	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	205	1 012	0 47	0 23	0 80	0 39
9 - 11 a m	192	1 012	0 33	0 17	0 67	0 35
11 a m - 1 p m	195	1 012	0 39	0 20	0 76	0 39
1 3 p m	208	1 011	0 29	0 14	0 79	0 38
3 5 p m	190	1 012	0 44	0 23	0 82	0 43
5 7 p m	215	1 013	0 43	0 20	0 99	0 46
7 - 9 p m	231	1 013	0 53	0 23	1 02	0 44
9 p m - 7 a m	960	1 011	1 43	0 17	4 13	0 43

*Summary*—Water Specific gravity fixed, volume partially so, Slight delayed response to noon meal Nitrogen Amount fixed Concentration somewhat fixed Fair response in normal time to noon meal Chlorid Concentration somewhat fixed, amount less so Slight, delayed response to noon meal

CASE 11—No 2074, male, aged 22, married Diagnosis Chronic nephritis Urine Acid, specific gravity, 1 009-1 014, albumin, 0 05 per cent to 0 04 per cent, no sugar Sediment Moderate number of hyaline and granular casts Blood Pressure 180-110 systolic, 140-80 diastolic

TABLE 21—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
1/ 2	18				
1/13	18				
1/20		0 088	238	5 68	0 046

TABLE 22—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/ 5	3 9	3 5	4 0	1 4	Fair excretion of added urea Poor excretion of added salt
1/ 6	3 9	4 8	4 0	0 9	
1/ 7	14 4	5 4	4 0	1 1	
1/ 8	3 9	5 8	4 0	0 8	
1/ 9	3 9	4 4	4 0	0 7	
1/10	3 9	4 6	4 0	0 8	
1/11	3 9	4 2	4 0	0 9	
1/12	3 9	5 6	4 0	0 9	
1/13			14 0	2 3	
1/14			4 0	2 3	
1/15			4 0	2 8	

TABLE 23—Two-Hour Renal Test

January 1	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	113	1 012	0 45	0 40	0 20	0 18
9 - 11 a m	80	1 012	0 54	0 67	0 16	0 20
11 a m - 1 p m	103	1 012	0 52	0 50	0 20	0 19
1 3 p m	107	1 012	0 50	0 47	0 26	0 24
3 - 5 p m	154	1 012	0 66	0 43	0 46	0 30
5 - 7 p m	135	1 012	0 45	0 33	0 45	0 33
7 9 p m	160	1 012	0 64	0 40	0 43	0 27
9 p m - 7 a m	450	1 012	1 67	0 37	1 08	0 24

*Summary*—Water Specific gravity fixed, volume not Medium response in normal time to noon meal Nitrogen Amount and percentage concentration moderately fixed Slight, delayed response to noon meal Salt Amount and percentage concentration moderately fixed Slight, delayed response to noon meal

CASE 12—No 2077, female, married, housewife Diagnosis Chronic nephritis, hypertension, chronic myocarditis Urine Acid, specific gravity, 1 013-1 020, albumin, slight to very slight trace, no sugar Sediment Rare hyaline and granular cast Blood Pressure 254-202 systolic, 140-110 diastolic

TABLE 24—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Differ- ence (McLean)	Alveolar CO <sub>2</sub> , mm
12/24	55					
12/28	45					
1/18	50					
1/19		0 225	6 45	5 85	0 13	
1/26						43 4



TABLE 25—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/11	11.1	6.6	4.0	1.6	Fair excretion of both added urea and salt, the former somewhat the better
1/12	11.1	4.9	4.0	2.0	
1/13	20.1	13.0	4.0	2.4	
1/14	11.0	6.7	4.0	1.0	
1/15	11.1	8.8	4.0	4.8	
1/16	11.0	5.5	14.0	6.3	
1/17	11.1	4.8	1.0	2.6	
1/18			4.0	3.4	
1/19			3.5	1.0	
1/20			3.0	2.8	
1/21			3.8	1.0	
1/22			3.8	1.4	
1/23			14.0	1.6	
1/24			4.0	7.6	
1/25			4.0	3.4	

TABLE 26—TWO-HOUR RENAL TEST

December 31	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	108	1.016	0.40	0.40	0.24	0.23
9-11 a m	72	1.017	0.90	1.20	0.22	0.30
11 a m - 1 p m	53	1.021	0.37	0.70	0.11	0.20
1-3 p m	114	1.020	1.48	1.30	0.42	0.37
3-5 p m	58	1.025	0.58	1.00	0.17	0.30
5-7 p m	68	1.023	1.70	2.50	0.22	0.32
7-9 p m	60	1.025	0.96	1.60	0.22	0.37
9 p m - 7 a m	230	1.026	2.76	1.20	1.11	0.44

*Summary*—Water No fixation of volume or specific gravity Medium response in normal time to noon meal Nitrogen No fixation of amount or percentage concentration Good response in normal time to noon meal Chlorid Moderate fixation of percentage concentration, less of amount Slight response in normal time to noon meal

CASE 13—No 2079, male, aged 23, single, student Diagnosis Chronic nephritis Urine Acid, specific gravity, 1 009-1 022, albumin, slightest possible trace to slight trace, no sugar Sediment No casts Blood Pressure 150-122 systolic, 90-60 diastolic

TABLE 27—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Urea N <sub>2</sub> of Blood, Gm per Liter
December 27	63 5	0 11

TABLE 28—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/31	11 0	11 0	4 0	2 0	Fair excretion of added urea Apparently poor excretion of added salt
1/ 1	11 0	10 0	4 0	2 6	
1/ 2	21 0	9 8	4 0	2 1	
1/ 3	11 0	12 0	4 0	2 0	
1/ 4	11 0	10 6	4 0	2 7	
1/ 5	11 0	9 8	14 0	5 5	

TABLE 29—Two-Hour RENAL TEST

December 30	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	72	1 020	0 86	1 20	0 11	0 15
9 - 11 a m	128	1 014	0 90	0 70	0 28	0 22
11 a m - 1 p m	76	1 022	1 14	1 50	0 18	0 22
1 - 3 p m	78	1 027	1 17	1 50	0 17	0 22
3 - 5 p m	80	1 027	1 31	1 64	0 26	0 32
5 - 7 p m	68	1 026	1 09	1 60	0 17	0 25
7 - 9 p m	68	1 027	1 09	1 61	0 19	0 28
9 p m - 7 a m	265	1 027	4 29	1 62	0 85	0 32

Summary—Water No fixation except that in the afternoon, which was both of volume and specific gravity No response to noon meal Nitrogen No fixation except in the percentage concentration during the afternoon Slight response in normal time to noon meal Chlorid Fixation both of amount and percentage concentration Very slight response in normal time to noon meal

CASE 14—No 2124, male, aged 54, married, driver Diagnosis Chronic nephritis, hypertension, chronic myocarditis Urine Acid, specific gravity, 1.013-1.016, albumin, none to very slight trace, no sugar Sediment, no casts Blood Pressure 250-200 systolic, 170-100 diastolic

TABLE 30—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean) Per Cent	Blood Chlorid, Gm per Liter
January 5	36	0.33		
January 11	28			
January 21		0.33	16	4.92*

\* Whole blood

TABLE 31—TWO-HOUR RENAL TEST

January 21	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	22	1.026	0.21	0.94	0.018	0.08
9-11 a m	44	1.026	0.58	1.20	0.026	0.06
11 a m-1 p m	57	1.026	0.68	1.20	0.034	0.06
1-3 p m	72	1.027	0.95	1.32	0.036	0.05
3-5 p m	78	1.027	0.89	1.14	0.047	0.06
5-7 p m	72	1.026	0.76	1.05	0.036	0.05
7-9 p m	162	1.020	1.18	0.70	0.324	0.20
9 p m-7 a m	945	1.016	3.78	0.40	3.78	0.40

*Summary*—Water Specific gravity fixed the greater part of the day, volume not Slight, delayed response to noon meal Nitrogen No fixation Slight response in normal time to noon meal Chlorid Both amount and percentage concentration fixed at a low level Very delayed response, but in good amount, to noon meal

CASE 15—No 2132, male, aged 35, single cashier Diagnosis Chronic nephritis, hypertension Urine Acid, specific gravity, 1.004-1.006, albumin, slight trace, no sugar Blood Pressure 270-240 systolic, 150-140 diastolic

TABLE 32—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLern), Per Cent	Blood Chlorid Gm per Liter	Chlorid Difference (McLean)
1/5	33				
1/8		0.296	9	5.7	0.01

TABLE 33—TWO-HOUR RENAL TEST

January 8	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	327	1 010	0 82	0 25	1 37	0 42
9-11 a m	100	1 011	0 50	0 50	0 23	0 23
11 a m - 1 p m	73	1 012	0 66	0 90	0 08	0 11
1-3 p m	156	1 012	0 62	0 40	0 359	0 23
3-5 p m	170	1 012	0 56	0 33	0 51	0 30
5-7 p m	149	1 012	0 54	0 36	0 358	0 24
7-9 p m	129	1 012	0 45	0 35	0 245	0 19
9 p m - 7 a m	655	1 011	2 29	0 35	1 97	0 30

*Summary*—Water Specific gravity fixed, volume not Good and prompt response to noon meal Nitrogen Amount fixed, percentage concentration not No response to noon meal Chlorid No fixation of salt Fair and prompt response to noon meal

CASE 16—No 2202, male, aged 49, single, painter Diagnosis Chronic nephritis, arteriosclerosis, hypertension Urine Acid, specific gravity 1 010-1 017, albumin very slight to slight trace, no sugar Sediment Few granular and hyaline casts Blood Pressure 240-170 systolic, 160-90 diastolic

TABLE 34—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Differ- ence (McLean)	Alveolar CO <sub>2</sub> , mm
1/21	18					
1/22						41 9
1/26		0 335	16 9	6 35	0 63	

TABLE 35—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/30	4 0	3 4	4 0	1 5	Poor response to both added urea and salt
1/31	4 2	3 9	4 0	1 4	
2/ 1	4 0	3 4	4 0	0 8	
2/ 2	14 0	5 0	4 0	1 6	
2/ 3	4 4	3 8	4 0	3 3	
2/ 4	4 0	3 8	4 0	2 6	
2/ 5	4 0	5 4	4 0	2 8	
2/ 6	4 0	4 0	14 0	3 8	
2/ 7	4 2	4 0	4 0	2 8	

TABLE 36—Two-Hour Renal Test

January 26	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	75	1 017	0 60	0 80	0 09	0 11
9 11 a m	68	1 015	0 53	0 80	0 14	0 20
11 a m - 1 p m	104	1 016	0 98	0 90	0 14	0 18
1 3 p m	105	1 017	0 72	0 70	0 20	0 20
3 - 5 p m	82	1 017	0 58	0 70	0 12	0 15
5 7 p m	112	1 016	0 68	0 60	0 25	0 25
7 - 9 p m	114	1 015	0 69	0 60	0 18	0 15
9 p m 7 a m	290	1 025	1 36	1 50	2 17	0 75

*Summary*—Water Specific gravity and volume moderately fixed Slight response in normal time to noon meal Nitrogen Amount and percentage concentration fixed Slight response in normal time to noon meal Chlorid Amount and percentage concentration fixed at a low level Slight response in normal time to noon meal

CASE 17—No 2218, female, aged 40, widow Diagnosis Chronic nephritis, chronic myocarditis, chronic bronchitis, hyperthyroidism, acute bronchitis Urine Acid, specific gravity, 1 014-1 023, albumin, none to trace, no sugar Sediment Occasional hyaline and rare granular cast Blood Pressure 184-160 systolic, 84-74 diastolic

TABLE 37—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
1/30	42				
2/18		0 191	81	6 1	0 217
2/23	50				

TABLE 38—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/24	11 0	9 4	4 0	2 6	Good response to added urea Fair response to added salt
2/25	11 0	7 6	4 0	2 8	
2/26	10 4	6 6	4 0	1 8	
2/27	18 4	17 0	4 0	3 0	
2/28	11 0	6 0	4 0	1 2	
3/ 1	9 4	5 5	3 9	1 0	
3/ 2	11 1	6 0	4 0	2 0	
3/ 3	11 0	4 8	14 0	3 0	
3/ 4	11 0	7 6	4 0	6 0	

TABLE 39—Two-Hour Renal Test

February 18	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	67	1 022	0 37	0 55	0 39	0 58
9-11 a m	74	1 020	0 28	0 31	0 50	0 68
11 a m-1 p m	56	1 022	0 40	0 72	0 25	0 44
1-3 p m	108	1 022	0 79	0 73	0 64	0 59
3-5 p m	100	1 023	0 76	0 76	0 60	0 60
5-7 p m	101	1 024	0 58	0 57	0 53	0 53
7-9 p m	22	1 024	0 33	1 50	0 11	0 48
9 p m-7 a m	245	1 023	0 75	0 31	1 00	0 41

*Summary*—Water Specific gravity fixed, volume not Good response in normal time to noon meal Nitrogen No fixation Medium response in normal time to noon meal Chlorid Both amount and percentage concentration fixed Medium response in normal time to noon meal

CASE 18—No 2237, female, aged 65, single, nurse Diagnosis Chronic nephritis, chronic myocarditis, arteriosclerosis, mitral insufficiency, dilatation of aorta Urine Acid, specific gravity 1 010-1 039, albumin, none to slight trace, no sugar Sediment Hyaline and rare granular cast Blood Pressure 188-115 systolic, 110-75 diastolic

TABLE 40—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
1/30	60				
2/ 8		0 123	42 0	6 40	0 381
2/24	56				
2/27		0 113	108 0	5 84	0 062
3/ 2		0 160	42 5	5 90	0 81

TABLE 41—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/14	11 0	9 5	4 0	2 2	Good response to added urea the first time, fair response the second. Fair response to added salt
2/15	11 0	3 4+	1 0	0 8+	
2/16	20 0	17 4	1 0	4 6	
2/17	11 0	5 6+	4 0	0 7+	
2/18	11 0	9 4	4 0	1 3	
2/19	9 9	8 0	14 0	5 0	
2/20	11 0	11 2	4 0	5 1	
2/21	11 0	8 0+	4 0	1 3+	
2/22	20 0	11 2	4 0	2 0	
2/23	11 0	7 0+	1 0	1 5+	

TABLE 42—TWO-HOUR RENAL TEST, MODIFIED

February 8	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	157	1 020	1 62	0 97	1 48	0 94
9 11 a m	107	1 019	0 56	0 52	1 09	1 02
11 a m - 1 p m	153	1 018	0 83	0 54	1 33	0 87
1 3 p m	114	1 026	0 75	0 66	1 21	1 06
3 5 p m	85	1 026	0 65	0 77	0 83	0 98
5 7 p m	115	1 022	0 63	0 55	0 95	0 83
7 - 9 p m	70	1 028	0 81	1 15	0 43	0 62
9 p m - 7 a m	237	1 028	2 37	1 00	1 59	0 67

*Summary*—No fixation. Water shows a medium response in normal time to noon meal. Nitrogen and salt are characterized by a slight response in normal time to noon meal.

CASE 18—No 2237 (continued)

TABLE 43—Two-Hour RENAL TEST, CASE 18

February 27	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	223	1 010	0 73	0 37	0 54	0 24
9-11 a m	72	1 016	0 57	0 79	0 30	0 42
11 a m - 1 p m	200	1 013	0 98	0 49	0 68	0 34
1-3 p m	75	1 022	0 90	1 20	0 34	0 45
3-5 p m	130	1 021	1 48	1 14	0 62	0 48
5-7 p m	89	1 020	0 96	1 08	0 25	0 28
7-9 p m	74	1 021	0 92	1 24	0 15	0 20
9 p m - 7 a m	317	1 023	4 42	1 39	1 08	0 34

*Summary*—No fixation Water shows a good response in normal time to noon meal, nitrogen a good response but delayed, salt a medium response in normal time

TABLE 44—Two-Hour RENAL TEST

March 2	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	264	1 010	0 96	0 37	0 60	0 23
9-11 a m	87	1 017	0 70	0 87	0 43	0 51
11 a m - 1 p m	67	1 017	0 64	0 92	0 26	0 37
1-3 p m	52	1 023	0 74	1 40	0 17	0 35
3-5 p m	84	1 025	0 85	1 59	0 36	0 42
5-7 p m	26	1 022	0 29	1 12	0 48	0 18
7-9 p m	55	1 027	0 78	1 40	0 19	0 35
9 p m - 7 a m	265	1 026	4 96	1 85	0 78	0 29

*Summary*—No fixation of water or nitrogen Very slight fixation of amount of salt, less of concentration Water Slight, delayed response to noon meal Nitrogen Medium, delayed response to noon meal Chlorid Medium, delayed response to noon meal



CASE 19—No 2246, male, aged 67, married, secretary Diagnosis Chronic nephritis and hypertension, dilatation of arch of aorta Urine acid, specific gravity, 1.015-1.021, albumin, very slight trace to large trace, no sugar Sediment No casts Blood Pressure 210-90 systolic

TABLE 45—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
1/30		0.20	18.2	6.55	0.76
1/31	21	0.18			
2/25	28				

TABLE 46—TWO-HOUR RENAL TEST

January 30	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grains	Per Cent	Grains	Per Cent
7-9 a m	18		0.14	0.80	0.11	0.60
9-11 a m	21		0.14	0.65	0.12	0.58
11 a m - 1 p m	29	1.034	0.23	0.80	0.10	0.56
1-3 p m	37	1.032	0.30	0.80	0.10	0.38
3-5 p m	30	1.032	0.30	1.00	0.08	0.28
5-7 p m	43	1.030	0.90	2.10	0.10	0.23
7-9 p m	46	1.030	0.55	1.20	0.08	0.18
9 p m - 7 a m	360	1.022	4.68	1.30	1.76	0.49

*Summary*—Water Amount fixed Specific gravity somewhat fixed Almost no response to noon meal Nitrogen Amount somewhat fixed, concentration not Fair, but delayed response to noon meal Chlorid Amount fixed, concentration not No response to noon meal

CASE 20—No 2292, female, aged 35, widow, clerk Diagnosis Chronic nephritis (?), neurasthenia Urine Acid, specific gravity, 1.009-1.027, albumin, none to slightest possible trace, no sugar Sediment No casts Blood Pressure 120-126 systolic, 84-92 diastolic

TABLE 47—FUNCTIONAL TESTS

Date	Blood Urea N <sub>2</sub> , Gm per Liter	Nitrogen Coefficient (Ambard)	Blood Chlorid, Gm per Liter
February 16	0.09		
February 18	0.11	0.061	5.85

TABLE 48—Two-Hour Renal Test ( $\frac{1}{2}$  Fluids) \*

February 19	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	37	1 021	0 26	0 70	0 17	0 46
9 - 11 a m	67	1 017	0 41	0 53	0 27	0 41
11 a m - 1 p m	91	1 015	0 42	0 46	0 32	0 35
1 3 p m	37	1 028	0 43	1 16	0 29	0 78
3 5 p m	41	1 028	0 66	1 62	0 28	0 68
5 - 7 p m	72	1 019	0 60	0 84	0 38	0 53
7 - 9 p m	39	1 022	0 64	1 64	0 17	0 44
9 p m 7 a m	152	1 025	2 49	1 64	0 61	0 40

\* Patient refused part of noon meal

*Summary*—Some fixation of total output of salt and nitrogen

CASE 21—No 2319, female, aged 42, married, housewife Diagnosis Chronic nephritis, hypertension, chronic tonsillitis Urine Acid, specific gravity, 1 010-1 027, albumin, none to a trace, no sugar Sediment Rare hyaline and granular cast Blood Pressure 240-164 systolic, 136-100 diastolic

TABLE 49—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
2/24	48				
2/27		0 10			
3/13	44				
3/17		0 12	99 5	5 94	0 138

TABLE 50—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/ 1	9 6	7 0	4 0	0 9	Fair excretion of added urea, poor excretion of added salt
3/ 2	11 0	9 5	4 0	4 4	
3/ 3	21 0	14 5	4 0	1 0	
3/ 4	11 0	5 5	4 0	0 8	
3/ 8	9 4	4 4	4 0	0 6	
3/ 9	9 7	5 6	3 6	1 2	
3/10	8 7	8 0	13 4	3 0	
3/11	11 0	9 5	4 0	3 5	

TABLE 51—TWO-HOUR RENAL TEST, MODIFIED

March 17	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	150	1.011	0.80	0.53	0.26	0.17
9-11 a m	152	1.010	0.68	0.45	0.33	0.22
11 a m-1 p m	57	1.016	0.55	0.96	0.23	0.41
1-3 p m	141	1.013	0.86	0.61	0.44	0.31
3-5 p m	72	1.018	0.71	0.99	0.34	0.47
5-7 p m	87	1.019	0.94	1.08	0.45	0.52
7-9 p m	63	1.020	0.73	1.16	0.32	0.50
9 p m-7 a m	220	1.026	3.30	1.50	1.01	0.46

*Summary*—Water No fixation Good and prompt response to noon meal  
 Nitrogen Very slight fixation of amount, considering the enforced modification of the nitrogen at the noon meal No fixation of concentration Fairly good and prompt response to noon meal Chlorid Amount fixed, concentration not Slight but prompt response to noon meal

CASE 22—No 2324, aged 45, single saleswoman Diagnosis Chronic nephritis, hypertension, arteriosclerosis, syphilis Urine Acid, specific gravity, 1.008-1.024, albumin, none to slight trace, no sugar Sediment Many hyaline and granular casts Blood Pressure 180-190 systolic, 95-58 diastolic

TABLE 52—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)	Alveolar CO <sub>2</sub> , mm
2/16		0.126		5.65		
2/18	43					
3/13	64					
3/25		0.093	65	5.93	0.259	
3/26	54					43.3

TABLE 53—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/11	39	20	40	10	Rather poor excretion of both added urea and salt
3/12	39	30	39	12	
3/13	140	64	39	28	
3/14	40	25	40	10	
3/15	34	34	40	15	
3/16	35	26	39	11	
3/17	141	35	41	10	
3/18	35	25	38	10	
3/19	40	20	39	09	
3/20	32	30	138	19	
3/21	26	20	30	19	
3/22	40	26	40	20	

TABLE 54—Two-Hour RENAL TEST

March 25	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	31	1 018	0 11	0 36	0 09	0 28
9 11 a m	50	1 012	0 25	0 50	0 09	0 19
11 a m 1 p m	110	1 011	0 30	0 27	0 28	0 25
1 - 3 p m	39	1 011	0 15	0 38	0 24	0 62
3 - 5 p m	14	1 036	0 25	1 80	0 07	0 52
5 - 7 p m	40	1 026	0 59	1 48	0 22	0 54
7 - 9 p m	48	1 021	0 35	0 73	0 24	0 49
9 p m - 7 a m	300	1 019	1 95	0 65	1 50	0 50

*Summary*—Water No fixation of volume or specific gravity Medium response in normal time to noon meal Nitrogen Some fixation of amount, none of percentage concentration Medium delayed response to noon meal Chlorid No fixation of amount or percentage concentration Slight response in normal time to noon meal

CASE 23—No 2336, aged 68, widow Diagnosis Chronic nephritis and hypertension, carcinoma of the stomach (?) Urine Acid, specific gravity, 1 008-1 022, albumin, none to very slight trace, no sugar Sediment Hyaline and rare granular cast Blood Pressure 218-168 systolic, 140-68 diastolic

TABLE 55—FUNCTIONAL TESTS

Date	Phthalein In 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
2/18	47	0 175	50	6 35	0 26
2/23		0 265	157	6 05	0 334
3/13	49				

TABLE 56—ADDED UREA AND SALT

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/28	60	50	40	14	In first test added nitro- gen was put out well, added salt fairly well In second test, with an intervening rheumatic fever, the ability to handle the added nitro- gen fell off The salt was excreted as before —only fairly well
3/ 1	46	46	30	06	
3/ 2	150	140	30	17	
3/ 3	86	120	35	17	
3/ 4	90	70	37	04	
3/ 5	84	78	138	10	
3/ 6	90	60	40	20	
3/ 7	110	64	14	26	
3/15	89	36	30	20	
3/16	58	55	25	24	
3/17	88	50	137	35	
3/18	90	65	40	57	
3/19	62	54	25	28	
3/20	179	74	30	28	
3/21	73	58	28	22	

TABLE 57—Two-Hour Renal Test, Modified

February 23	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	120	1 009	0 54	0 45	0 13	0 11
9 - 11 a m	122	1 010	0 61	0 50	0 22	0 18
11 a m 1 p m	56	1 012	0 39	0 69	0 73	0 13
1 - 3 p m	50	1 017	0 50	0 99	0 10	0 19
3 - 5 p m	33	1 022	0 34	1 04	0 08	0 24
5 - 7 p m	47	1 016	0 36	0 77	0 11	0 23
7 - 9 p m	40	1 022	0 49	1 22	0 12	0 31
9 p m - 7 a m	192	1 021	2 30	1 20	0 53	0 30

*Summary*—Water No fixation of volume or specific gravity Slight, delayed response to noon meal Nitrogen Amount somewhat fixed, concentration not Slight response in normal time to noon meal Chlorid Amount and concentration somewhat fixed Slight, delayed response to noon meal

CASE 24 — No 2357, male, aged 52, married, piano mover Diagnosis Chronic nephritis and hypertension, chronic myocarditis Urine Alkaline; specific gravity, 1 010-1 027, albumin, none to very slight trace, no sugar Blood Pressure 210-180 systolic, 130-100 diastolic

TABLE 58—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Blood Chlorid,* Gm per Liter
February 18	52		
February 19		0 397	4 391

\* Whole blood

TABLE 59—Two-Hour Renal Test

March 2	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	123	1 021	0 96	0 48	1 09	0 89
9 - 11 a m	118	1 020	0 67	0 57	1 10	0 93
11 a m 1 p m	133	1 021	0 94	0 71	1 16	0 87
1 - 3 p m	125	1 024	1 15	0 92	1 14	0 91
3 - 5 p m	120	1 022	1 42	1 18	0 98	0 82
5 - 7 p m	108	1 022	1 53	1 42	0 94	0 87
7 9 p m	106	1 021	1 08	1 02	0 90	0 85
9 p m - 7 a m	327	1 023	3 98	1 22	2 29	0 70

*Summary*—Water Fixation of output and specific gravity No response to noon meal Nitrogen No fixation Fair but delayed response to noon meal Salt Fixation of output and concentration No response to noon meal

CASE 25—No 2428, male, aged 60, married, policeman Diagnosis Chronic nephritis and hypertension Urine Acid, specific gravity, 1 015-1 025, albumin, none to trace, no sugar Sediment No casts Blood Pressure 205-150 systolic, 145-95 diastolic

TABLE 60—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)	Alveolar CO <sub>2</sub> , mm
3/ 3						38 6
3/ 5	50					
3/14	61					
3/16		0 228	80 7	6 24	0 52	

TABLE 61—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/17	11 0	9 2	4 0	1 6	Fair response to added urea. Added salt test not made. Apparently some inability to handle salt.
3/18	11 0	7 8	4 0	1 8	
3/19	21 0	9 6	4 0	1 4	
3/20	11 0	9 4	4 0	1 6	

TABLE 62—TWO-HOUR RENAL TEST

March 16	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	33	1 028	0 57	1 74	0 05	0 16
9 11 a m	56	1 026	0 97	1 74	0 15	0 26
11 a m 1 p m	96	1 023	1 40	1 46	0 25	0 36
1 3 p m	68	1 026	1 16	1 70	0 29	0 42
3 5 p m	120	1 026	1 81	1 51	0 80	0 67
5 7 p m	78	1 023	1 05	1 34	0 62	0 61
7 9 p m	50	1 028	0 53	1 05	0 25	0 49
9 p m 7 a m	220	1 027	3 41	1 55	1 43	0 65

Summary—Water Specific gravity fixed, volume not Moderate but delayed response to noon meal Nitrogen No fixation Good and prompt response to noon meal Chlorid No fixation Slight, delayed response to noon meal

CASE 26—No 2429, male, aged 45, married, teamster      Diagnosis      Chronic  
nephritis, hypertension, chronic myocarditis, auricular fibrillation      Urine  
Acid, specific gravity, 1.021, trace of albumin, no sugar      Sediment      No casts  
Blood Pressure      165-125 systolic, 120-90 diastolic

TABLE 63—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/ 5	39	0.1875			
3/ 8					
3/ 9	41				
3/26	61	0.12	65	6.25	0.44
3/30					

TABLE 64—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/18	11.0	12.4	4.0	4.8	Good response to added urea, poor response to added salt
3/19	10.9	9.4	4.0	5.5	
3/20	21.0	17.8	4.0	3.8	
3/21	11.0	12.2	4.0	2.8	
3/22	10.8	7.8	4.0	2.4	
3/23	11.2	14.6	4.0	2.6	
3/24	10.8	13.4	4.0	1.8	
3/25	9.8	5.8	4.0	1.1	
3/26	10.6	12.2	14.0	3.8	
3/27	10.4	11.0	4.0	2.8	



TABLE 65—Two-Hour Renal Test

March 30	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	65	1 025	1 14	1 75	0 29	0 45
9 11 a m	66	1 028	1 08	1 63	0 41	0 63
11 a m 1 p m	62	1 030	1 07	1 72	0 35	0 56
1 - 3 p m	83	1 030	1 13	1 48	0 50	0 60
3 5 p m	98	1 029	1 28	1 39	0 53	0 65
5 7 p m	75	1 030	1 37	1 82	0 47	0 62
7 - 9 p m	66	1 032	1 23	1 86	0 36	0 55
9 p m 7 a m	216	1 029	4 49	2 03	1 19	0 55

*Summary*—Water Fixation of volume and specific gravity with slight, delayed response to noon meal Nitrogen Fixation of amount and percentage concentration with slight, delayed response to noon meal Chlorid Fixation of amount and percentage concentration with slight delayed response to noon meal

CASE 27—No 2438, male, aged 35, single, blacksmith Diagnosis Chronic nephritis, hypertension, hemiplegia Urine Acid, specific gravity, 1 010-1 015, albumin 0 8 gm to 7 0 gm per liter, no sugar Sediment Occasional hyaline and granular cast Blood Pressure 140-155 systolic, 100-105 diastolic

TABLE 66—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Nonprotein N <sub>2</sub> of Blood, Gm per Liter
March 7	27	0 39
March 10		
March 13	27	
April 2	32	

TABLE 67—TWO-HOUR RENAL TEST

March 10	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	51	1 020	0 86	1 69	0 48	0 94
9 - 11 a m	63	1 020	0 81	1 29	0 60	0 96
11 a m - 1 p m	67	1 020	1 09	1 62	0 62	0 92
1 - 3 p m	77	1 021	1 17	1 52	0 69	0 90
3 - 5 p m	95	1 021	1 50	1 58	0 86	0 90
5 - 7 p m	91	1 020	2 53	2 78	0 82	0 90
7 - 9 p m	87	1 021	1 17	1 34	0 78	0 90
9 p m - 7 a m	477	1 020	9 59	2 01	3 82	0 80

*Summary*—Water Fixation of output and specific gravity Slight response, somewhat delayed, to noon meal Nitrogen No fixation Good response, somewhat delayed, to noon meal Salt Fixation of output and concentration Slight response, somewhat delayed, to noon meal

CASE 28—No 2444, aged 15, schoolboy Diagnosis Chronic nephritis (?)  
 Urine Acid, specific gravity, 1 011-1 015, albumin, trace to 3 gm per liter,  
 no sugar Sediment Rare granular cast Blood Pressure 140-110 systolic,  
 80-72 diastolic

TABLE 68—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/ 7	62				
3/26	61	0 106	605	5 99	0 041

TABLE 69—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/21	11 0	8 4	4 0	1 4	Good response to added urea, poor response to added salt
3/22	10 9	5 5	4 0	1 1	
3/23	11 1	9 4	14 0	2 9	
3/24	10 9	8 4	4 0	4 2	
3/25	9 8	6 1	4 0	1 6	
3/26	10 7	7 2	4 0	1 6	
3/27	21 0	21 0	4 0	3 2	
3/28	11 0	7 7	4 0	0 8	
3/29	11 2	8 3	4 0	6 8	

TABLE 70—Two-Hour Renal Test

March 13	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	415	1 011	1 66	0 40	1 53	0 37
9 11 a m	365	1 010	2 04	0 56	1 31	0 36
11 a m - 1 p m	142	1 018	1 12	0 79	0 54	0 38
1 3 p m	153	1 021	1 64	1 07	1 01	0 66
3 5 p m	124	1 020	1 14	0 92	0 81	0 65
5 7 p m	240	1 013	1 20	0 50	1 08	0 45
7 9 p m	56	1 022	0 69	1 28	0 60	0 47
9 p m 7 a m	167	1 026	2 46	1 49	0 66	0 40

Summary—Water No fixation Medium, delayed response to noon meal  
 Nitrogen No fixation Medium, prompt response to noon meal Chlorid  
 No fixation Slight but prompt response to noon meal

CASE 29—No 2449, female, aged 18, single Diagnosis Chronic nephritis  
 and hypertension Urine Acid, specific gravity, 1 008-1 016, albumin, trace  
 to large trace, no sugar Sediment Very rare hyaline cast Blood Pressure  
 258-218 systolic, 174-150 diastolic

TABLE 71—FUNCTIONAL TESTS

Date	Phthalein In 2 Hours, Per Cent	Blood Urea N., Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/9	3				
3/19		0 695	16 2	6 55	0 77

TABLE 72—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/10	3 4	3 0	3 8	3 1	Poor response to both added urea and salt, particularly the latter
3/11	3 6	3 6	4 0	2 6	
3/12	2 0	3 6	2 0	3 0	
3/13	13 8	5 1	4 0	2 8	
3/14	4 0	4 0	4 2	2 4	
3/15	4 5	3 6	4 0	1 6	
3/16	3 0	3 8	13 4	3 0	
3/17	2 9	3 8	2 0	3 0	
3/18	3 8	4 7	4 0	2 6	

TABLE 73—Two-Hour Renal Test

March 19	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	47	1 012	0 21	0 45	0 06	0 14
9 - 11 a m	58	1 011	0 23	0 49	0 16	0 24
11 a m - 1 p m	98	1 010	0 27	0 28	0 25	0 26
1 3 p m	108	1 010	0 37	0 34	0 37	0 34
3 5 p m	73	1 011	0 32	0 44	0 18	0 25
5 7 p m	61	1 010	0 31	0 50	0 13	0 21
7 - 9 p m	74	1 010	0 35	0 47	0 19	0 25
9 p m 7 a m	430	1 009	1 81	0 42	1 12	0 26

*Summary*—Fixation of all elements, both total output and percentage concentration Slight response in normal time to noon meal in all elements

CASE 30—No 2473, female aged 41, married, housewife Diagnosis Chronic nephritis, hypertension, ventral hernia Urine Acid, specific gravity, 1 010-1 018 albumin, none to very slight trace, no sugar Sediment Rare hyaline and granular cast Blood Pressure 208-172 systolic, 115-83 diastolic

TABLE 74—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/15	55				
3/20		0 098	159	6 75	0 125
3/24	59				
4/ 9	65				

TABLE 75—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
4 9	11 0	9 0	4 0	1 6	Good response to added urea, poor response to added salt
4/10	11 0	6 4	4 0	0 9	
4/11	21 0	14 5	4 0	1 0	
4/12	11 0	9 4	4 0	1 9	
4/13	11 0	5 2	4 0	1 8	
4/14	6 0	3 5	14 0	4 9	
4/15	11 0	4 1	4 0	0 8	

TABLE 76—Two-Hour Renal Test

April 20	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	80	1 017	0 65	0 81	0 06	0 08
9 11 a m	50	1 015	0 53	1 05	0 04	0 08
11 1 m - 1 p m	12	1 020	0 54	1 23	0 03	0 08
1 3 p m	40	1 025	0 67	1 64	0 02	0 04
3 5 p m	52	1 025	0 83	1 60	0 04	0 08
5 7 p m	123	1 018	1 18	0 96	0 23	0 23
7 9 p m	108	1 020	0 94	0 87	0 42	0 39
9 p m 7 a m	320	1 021	3 01	0 91	1 06	0 33

*Summary*—Water Shows no fixation Medium, delayed response to noon meal Nitrogen Shows no fixation Medium, delayed response to noon meal Chlorid Shows suggestion of fixation in both amount and concentration Slight, delayed response to noon meal

CASE 31—No 2486, male, aged 63, single Diagnosis Chronic nephritis, hypertension, arteriosclerosis, dilatation of aortic arch Urine Acid, specific gravity, 1 010-1 015, albumin, slight trace to 2 5 gm per liter, no sugar Sediment Occasional hyaline and granular cast Blood Pressure 210-140 systolic, 110-84 diastolic

TABLE 77—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/14	13				
3/17		0 61	5 9	6 3	0 571
3/26	12				

TABLE 78—ADDED URFA AND SALT

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/25	10 8	10 4	4 0	2 5	Fair response to added salt Apparently able to handle nitrogen pretty well
	11 0	9 7	4 0	2 7	
	10 9	7 6	14 0	3 4	
	11 0	12 5	4 0	5 8	
	21 0	Lost	4 0	Lost	

TABLE 79—Two-Hour Renal Test

March 17	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	61	1 017	0 50	0 82	0 098	0 16
9 - 11 a m	87	1 018	0 76	0 87	0 19	0 22
11 a m - 1 p m	107	1 019	0 88	0 82	0 25	0 23
1 - 3 p m	113	1 018	0 90	0 80	0 26	0 23
3 - 5 p m	135	1 018	1 12	0 83	0 41	0 30
5 - 7 p m	127	1 017	1 10	0 87	0 41	0 32
7 - 9 p m	97	1 018	0 79	0 81	0 19	0 20
9 p m - 7 a m	38	1 020	0 30	0 80	0 17	0 44

*Summary*—Water Slight fixation of volume, moderate fixation of specific gravity Slight, delayed response to noon meal Nitrogen Well-marked fixation of percentage concentration Slight, delayed response to noon meal Chlorid Fixation of both amount and percentage concentration Slight, delayed response to noon meal

CASE 32—No 2512, female 55, single, housekeeper Diagnosis Chronic nephritis, hypertension, aphasia Urine Acid, specific gravity 1 006-1 022, albumin, none to very slight trace, no sugar Sediment Rare hyaline cast Blood Pressure 250-142 systolic, 100-65 diastolic

TABLE 80—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/22	49				
4/ 5		0 125	77	6 43	0 615
4/ 7	60				
4/30	57				

TABLE 81—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/23	3 0	5 5	4 0	1 0	Good response to added urea, poor response to added salt
3/24	4 2	4 0	4 0	0 9	
3/25	13 5	10 6	4 0	0 9	
3/26	4 0	6 4	4 0	1 0	
3/27	4 1	5 4	4 0	1 1	
3/28	4 1	4 6	4 0	1 0	
3/29	4 0	4 7	14 0	3 4	
3/30	4 0	4 5	4 0	4 0	

TABLE 82—Two-Hour Renal Test

April 5	Water, cc	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 9 a m	252	1 009	0 45	0 18	0 45	0 18
9 11 a m	150	1 009	0 38	0 25	0 44	0 29
11 a m - 1 p m	143	1 010	0 40	0 23	0 27	0 19
1 3 p m	143	1 010	0 43	0 20	0 21	0 15
3 5 p m	79	1 017	0 40	0 51	0 21	0 27
5 - 7 p m	105	1 019	0 62	0 59	0 51	0 49
7 9 p m	73	1 018	0 50	0 63	0 38	0 52
9 p m 7 a m	233	1 022	1 64	0 71	1 37	0 79

Summary—Water No fixation of volume or specific gravity Slight, delayed response to noon meal Nitrogen Slight fixation of amount Slight, delayed response to noon meal Chlorid Slight fixation of amount Slight, delayed response to noon meal

CASE 33—No 2548, 33 female, married, housewife Diagnosis Nephritis subacute, of pregnancy Urine Acid, specific gravity 1 006-1 020, albumin, very slight trace, no sugar Sediment Very rare hyaline, granular and cellular cast Rare red blood corpuscle Blood Pressure 158-118 systolic, 98-66 diastolic

TABLE 83—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N., Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/28	65				
3/29		0 094	215	5 9	0 207
4/ 3	55				
4/14	52				

TABLE 84—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
4/1	11 0	8 6	4 0	2 2	Good response to added urea, poor response to added salt
4/2	9 8	7 6	4 0	2 2	
4/3	21 0	17 0	4 0	2 6	
4/4	10 9	11 0	4 0	2 2	
4/5	10 8	10 5	4 0	1 4	
4/6	10 7	5 6	4 0	1 1	
4/7	10 0	13 0	14 0	4 0	
4/8	11 0	9 6	4 0	4 0	

TABLE 85—Two-Hour Renal Test

March 29	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7 - 9 a m	164	1 010	0 87	0 53	0 15	0 09
9 - 11 a m	75	1 015	0 53	0 71	0 10	0 13
11 a m - 1 p m	193	1 008	0 63	0 33	0 17	0 09
1 - 3 p m	48	1 025	0 67	1 42	0 16	0 33
3 - 5 p m	64	1 018	0 70	1 10	0 09	0 14
5 - 7 p m	80	1 022	2 14	2 68	0 23	0 29
7 - 9 p m	48	1 023	0 50	1 05	0 05	0 10
9 p m 7 a m	265	1 026	5 57	2 10	0 45	0 17

*Summary*—Water No fixation Good and prompt response to noon meal  
 Nitrogen No fixation Good but delayed response to noon meal Salt Amount  
 fixed, concentration not Practically no response to noon meal

CASE 34—No 2567, male, 30, married, enamel worker Diagnosis Chronic  
 nephritis, hypertension, chronic valvular disease, mitral insufficiency, albumin-  
 uric retinitis Urine Acid, specific gravity 1 006-1 011, albumin, 2 to 3 5 gm  
 per liter, no sugar Sediment Many hyaline and granular casts Blood Pres-  
 sure 195-170 systolic, 145-140 diastolic

TABLE 86—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent	Blood Urea N <sub>2</sub> , Gm per Liter	Urea Index (McLean), Per Cent	Blood Chlorid, Gm per Liter	Chlorid Difference (McLean)
3/30	Trace				
4/ 5		0 575	5	6 18	0 422

TABLE 87—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/ 7	11 0	8 9	4 0	2 2	Apparently a good re sponse to added urea, but a poor one to added salt
3/ 8	11 0	9 1	4 0	2 3	
3/ 9	11 0	12 2	4 0	2 8	
3/10	21 0	Lost	4 0	Lost	
3/11	11 0	15 5	4 0	2 4	
3/12	11 0	6 9	4 0	1 4	
3/13	11 0	9 8	4 0	1 4	
3/14	11 0	10 0	4 0	1 4	
3/15	11 0	13 4	4 0	1 4	
3/16	11 0	9 4	14 0	1 8	



TABLE 88—Two-Hour Renal Test

April 5	Water, c c	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent	Grams	Per Cent
7-9 a m	85	1 017	0 68	0 80	0 07	0 07
9-11 a m	67	1 017	0 54	0 84	0 07	0 07
11 a m 1 p m	78	1 017	0 70	0 90	0 08	0 10
1-3 p m	78	1 017	0 65	0 85	0 10	0 15
3-5 p m	104	1 017	0 83	0 80	0 17	0 17
5-7 p m	110	1 016	0 75	0 68	0 25	0 23
7-9 p m	125	1 016	0 79	0 65	0 26	0 22
9 p m 7 a m	520	1 015	2 91	0 57	1 05	0 20

*Summary*—Water Amount and specific gravity moderately fixed Slight, delayed response to noon meal Nitrogen Amount and percentage concentration both fixed Slight, delayed response to noon meal Salt Amount and percentage concentration fixed at a low level Slight delayed response to noon meal

## RESULTS OF THE TWO-HOUR RENAL TEST

An analysis of the results given above for the cases of nephritis shows that the curves of water, nitrogen and chlorid excretion in a given case are on the whole, very similar This is especially true in the comparison of the curves of water and chlorid output Twenty-six out of thirty-two curves analyzed are almost complete counterparts as far as these two factors go The remaining six are almost parallel, two being completely so in the afternoon This would tend to show that, in the diseased kidney at least, water and salt obey very similar laws of excretion The water and nitrogen curves are not so closely parallel However, in thirteen out of twenty-six cases they are nearly parallel and in only two of the remaining thirteen are they very different

With the two-hour renal test the diseased kidney shows its loss of function in several different ways, dependent on the severity of the case Any combination of the following may be obtained There may be general lowered excretion of water, nitrogen and salt throughout the test As is expected, the very low outputs occur in the more severe types There may be hypersensitivity In certain mild cases the kidneys show hypersensitivity, especially in the morning, by putting out an abnormal amount of any or all of these elements for one or two periods This is frequently associated with an afternoon fatigue In cases displaying this latter condition the kidneys seem to do fairly well until they are crowded by the products of the heavy noon meal Of course, the severe cases show fatigue all the time, if you wish to call it such But I am referring here particularly to the mild cases that com-

ply with the foregoing. Then there may be a decreased or delayed response to the noon meal or there may be fixation, more or less complete, in the curve of excretion of any or all three elements. In these cases the power of excretion is fixed at a definite level and even the large noon meal cannot increase the height of this level. As a result we have a flattening out of the various curves.

With these possibilities in mind let us see what our cases have shown by the two-hour renal test.

#### WATER EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

The output of water in thirteen out of thirty-two tests performed on cases of nephritis (41 per cent) approached fairly closely to the normal. These cases on the whole were of a fairly mild type or were complicated by cardiac conditions. Five out of the thirty-two tests showed a very moderate, and fourteen, a distinctly low, output. The larger number of the cases, therefore, showed a lowered excretion of water. Only two cases showed well-marked hypersensitivity. Five showed a distinct afternoon fatigue. Nineteen out of thirty-two (59 per cent) showed a slight response to the noon meal, ten (31 per cent) a medium response, and only three (9 per cent) a good one. Twenty cases (63 per cent) were characterized by a distinct delay in the time of response, whereas twelve (37 per cent) were normal in this respect. The large majority of those showing a medium or slight response were characterized also by a delayed response.

Ten out of thirty-two tests (30 per cent) showed a distinct fixation of both volume and specific gravity. Six (19 per cent) showed a fixation of specific gravity with more or less variation in volume. In these, the concentration power was apparently impaired. In this group it was noticed that the two most severe cases showed a fixation at a low level, whereas the other four, which were less severe or were complicated by myocarditis, showed a fixation at a higher level. Another group of two cases showed a somewhat different condition. In these the volume remained fixed but the specific gravity varied. Here the concentrating function was apparently preserved. One of these (and possibly both) was a case of myocardial insufficiency. A group of fourteen (44 per cent) all comparatively mild, showed no fixation whatsoever.

#### SALT EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

The large majority of the curves, from cases of nephritis, twenty-six out of thirty-two (81 per cent), showed a low output of sodium chlorid. This is a considerably greater number than those with low water excretion. Five (16 per cent) showed a medium, and only one

(3 per cent) a high, excretion of salt. Three showed definite hypersensitivity. Ten (31 per cent) tired in putting out the salt during the afternoon. With regard to the noon meal, in twenty-six cases (81 per cent) there was only a slight response. In six the response was medium, and in none was it normal. Twenty cases (63 per cent) showed a distinct delay in response to the large noon meal. Seventeen out of thirty-two showed almost complete fixation both of amount and percentage concentration of salt. Most of these, too, had a low output and low concentration. In nine there was a fixed amount but a varying percentage, in all but one of these the fixation was low. These retained, at least to a certain degree, their power of salt concentration. Only five showed no fixation whatsoever. This is in contrast to fourteen cases in which the water output showed no fixation.

#### NITROGEN EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

Nitrogen excretion seems to be much less affected than either salt or water excretion. Only twenty-six determinations were made. Eight showed a low, eleven a medium, and seven a fairly normal, output. Four displayed fairly well marked hypersensitivity. Only five showed afternoon fatigue. Fourteen patients showed only a slight response to the noon meal, seven a medium, and five a good, response. In seventeen cases there was a distinct delay in putting out the increased nitrogen ingested at the noon meal. The rest were normal. Only seven cases were characterized by marked fixation. These were the most severe cases studied. Six showed a fixation of amount but not of concentration. In thirteen there was no fixation at all.

#### DISCUSSION OF EXCRETION OF WATER, SALT AND NITROGEN AS SHOWN IN THE TWO-HOUR RENAL TEST

As can be seen from the foregoing, the chlorid excretion of the kidney is more seriously, and presumably more quickly, affected than either of the other two functions. The excretion of water and total solids runs fairly close to the chlorid excretion. The ability of the kidney to handle nitrogen however, seems to be maintained considerably longer than the other two elements. This bears out our observations in other tests that the excretion of salt is usually impaired sooner than that of nitrogen, and that when both are affected in a given case the impairment of the nitrogen excretion is less marked than that of the salt.

We have been led to believe that the most significant parts of the test are the response to the noon meal and the degree of fixation in the curves. However, the delicacy of the test is vouched for by the fact that not a single case of chronic nephritis, no matter how mild, failed

to show in one or more elements (water, salt and nitrogen) some disturbance of function such as hypersensitivity, fatigue, etc. Many of the milder cases, too, were normal in function as far as other tests like the phenolsulphonephthalein, blood urea, etc., could indicate. However, it must be borne in mind that normal cases may show, temporarily at least, these slight disturbances of function.

Putting the various curves in each case together, certain observations as to the severity of the disease can be made out. As to the amount of response, seven of the nine cases that showed only a slight response in all three elements were severe. The time of response seemed less important. Seven showed a delayed response in all three elements. Two of our most severe cases, however, showed no delay whatsoever, and three that did show delay were comparatively mild.

Fixation seems to be the most important part of this test. From the point of view of fixation in all three elements, it is seen that in our six worst cases the fixation was marked in both amount and percentage concentration. In only two was there no fixation whatsoever. These were extremely mild cases. Even in these, however, the test showed abnormal function by afternoon fatigue, delayed response, etc. Between these two groups of extremes, the cases display varying amounts of fixation in excretion of one or more elements—the more severe the greater the fixation.

It was thought that those cases complicated by cardiac conditions might be characterized in a special way. This, however, was not found to be true always. Some did show a high level of fixation in volume of urine and specific gravity with a low level of concentration and amount of sodium chlorid. These may have been more truly cases of myocardial insufficiency with added renal involvement. However, we were not convinced that this was characteristic of cardio-renal cases.

The test is by no means without faults. The most important is that it cannot be used in all cases of chronic nephritis. In very severe cases, of course, no such diet can be taken even when the heavy noon meal is modified, as was done by us for some patients. This, of course, may interfere more or less with our results, inasmuch as the reduction in the meal may just fail to show fixation when the full meal would do so.

In some cases the patient is made temporarily worse by the full diet. Then, too, digestive disturbances, indicated by distress after the noon meal, may cause a delayed absorption in the stomach and intestines. The various elements then get to the kidneys slowly and in small amounts. This would, of course, interfere with the proper interpretation of results. Cases with edema cannot be studied very satisfactorily because of the unstable water metabolism.

COMPARISON OF TWO-HOUR RENAL TEST AND ADDED UREA  
AND SALT TEST

To try out the comparative efficiency of the two-hour renal test and the added urea and salt test and to see if the former could supplant the latter, we can compare the results of both tests made on the same patient in twenty-one cases of chronic nephritis. Of these, five had no nitrogen determinations in the two-hour test because at that time we were not quantitating the nitrogen.

The very nature of the tests prevented their being done synchronously. The two-hour renal test was usually made either just before or just after the other test. As a result there were frequently several days between the two tests. Despite this fact, however, there was a surprisingly close parallelism between the results obtained by both methods. Of the twenty-one cases all but two showed pretty complete agreement in all phases. One of these (Case 26) showed an excellent response to added urea but a distinct fixation of nitrogen output in the two-hour test. The fixation, however, was at a high level and may have been accounted for by the fact that the patient had at this time a changed circulation from chronic myocarditis and auricular fibrillation. (McLean's urea index showed fair ability to handle nitrogen.) The second case (Case 32) showed the same functional result. The patient had been on a low-protein diet preceding the added urea. This may have caused a temporary improvement in her nitrogen function, which had again become weaker when the two-hour renal test was made about one week later. (In this case, too, McLean's urea index showed fair ability of the kidney to handle nitrogen.)

COMPARISON OF THE DIETARY TESTS WITH THE INDICES OF  
NITROGEN AND SALT EXCRETION

The objections to these dietary tests cited above make it evident that they are not entirely satisfactory. The methods of obtaining the indices of urea and salt excretion as worked out by Ambard and McLean and others obviate many of these difficulties because they do not necessitate fixed diets and prolonged quantitative observations. It is interesting to see how the results obtained from the dietary tests compare with those furnished by the indices of excretion. In fifteen patients both of the dietary tests were made and the indices of excretion were calculated. In addition, the phenolsulphonephthalein excretion was observed. The blood urea-nitrogen and the blood chlorid figures were known so that these might be used to check up the value of the other methods.

Of course a comparison of such results presents many difficulties but a study of these cases (Cases 11, 12, 16, 17, 18, 22, 23, 25, 26, 28, 29, 30, 31, 32 and 34) will show how far the various tests agree and to

a certain extent which test seems to give uniformly the best index of the condition of the patient as judged from the sum total of observations on the patient. The phenolsulphonephthalein output and blood urea figures seem to agree pretty well. In a number of cases they are almost normal and yet the other tests give evidence of functional disturbance.

The question of the comparative values of these tests narrows itself down to a determination of whether the shorter and simpler nitrogen and salt tests of Ambard or McLean are as satisfactory as the more difficult and complex dietary tests of von Monakow and Hedinger and Schlager. When we compare these tests in our group of cases we note that in two cases (Cases 11 and 18, March 2) the two-hour renal test shows us a greater disturbance of salt excretion than is indicated by the indices of excretion. However, the difference is marked only in one. On the other hand in two more cases (Cases 25 and 32) the opposite effect is noted, the indices of excretion indicating a greater impairment of function. With regard to nitrogen function we find that in only one (Case 11) does the two-hour renal test show greater renal disturbance than does the index of urea excretion. The determination of the index of excretion brings out distinctly greater loss of function in six other cases than is indicated by the dietary tests. In the other patients the results of the two tests are about the same.

It would seem from this that the indices of urea and salt excretion, especially the former, as determined by Ambard's or McLean's formulas, are more satisfactory tests of renal function than the others here referred to, as they give us as much information as any of the other tests, especially in the milder cases, they are distinctly shorter than the dietary tests since they can be completed in two hours, if necessary, and they are not especially difficult to carry out. The phenolsulphonephthalein excretion, to be sure, is less difficult of determination than any of these but it is by no means as satisfactory in cases of chronic nephritis because in the earlier stages of the condition it may be essentially normal although there are definite disturbances in salt, nitrogen or water excretion. A simple determination of blood nitrogen similarly may give normal figures in milder cases, while the calculated index of excretion is distinctly abnormal. For the determination of these indices of excretion no dieting or preliminary preparation is required and the determinations can be made on all but moribund patients. Hence they have an advantage over the longer dietary tests. More investigation, however, is still needed for a proper understanding of a number of factors which seem to influence the index of excretion apart from the renal lesion. One of these factors is the influence of the amount of water excretion on the index of excretion of urea or salt in a given individual. This phase of the subject is at present under

investigation The factors which lead to very high indices of urea excretion too are not thoroughly understood at present These and other points must be studied before the indices of excretion can be used with complete satisfaction in the study and subsequent dietary arrangement of our cases of chronic nephritis

#### SUMMARY

Several methods have been proposed for the study of salt and nitrogen excretion in chronic nephritis In one method, with the patient on a standard diet, the elimination of an added amount of salt and nitrogen is followed for several days, in another, the salt and nitrogen excretion is quantitated for one day in two-hour urine specimens with the patient on several standard meals of varying composition A third way is to quantitate salt and nitrogen in the blood and urine and express their relations by a formula giving an index of excretion In thirty cases the first two tests have been carried out along with other tests of renal function The second, or two-hour renal test as we have called it, requires a shorter observation in the hospital and the main part of the test occupies only twenty-four hours of the patient's time, while the first, or added urea and salt test, requires ten or twelve days of hospital observation on a standard diet The shorter test appears to yield almost the same facts as the longer In general, salt excretion is impaired before there is much disturbance of water and nitrogen excretion, in most patients salt and water excretion behave very similarly, the nitrogen excretion is greatly impaired usually only in the severe cases Salt, water and nitrogen excretion show some disturbance in even the very mild cases in which phenolsulphonephthalein excretion is normal, and there is no increased blood nitrogen These dietary tests can not be used in all cases of chronic nephritis They cannot be carried out in those that are very severe The methods involving the determinations of the indices of excretion of urea and salt do not have a number of the difficulties met with in carrying out the dietary tests These indices were determined in fifteen cases in which both dietary tests were carried out, and the indices seemed to give as much information as the other tests and to possess distinct advantages inasmuch as they can be determined for practically every patient and require considerably less time and less labor in their execution The great advantage of all three of these tests is that they give information as to disturbed renal function in those mild cases in which phenolsulphonephthalein excretion is normal and the blood urea-nitrogen is not increased

## EXPERIMENTAL HYPERCHOLESTEROLEMIA \*

KAETHE DEWEY, M D

CHICAGO

In previous experimental work<sup>1</sup> a watery colloid emulsion of cholesterol was used and proved to be such a satisfactory preparation for intraperitoneal injections in rabbits and guinea-pigs, that I employed it again as most suitable for producing a direct hypercholesterolemia. The use of such emulsions eliminates some of the objectionable features attending the prevalent method of administering cholesterol by feeding. The necessity of resorting to solvents such as fats and oils involves the production of a fat infiltration which, although not considered as pathological necessarily masks the effects of cholesterol on the tissues to some extent and complicates the conclusions.

Instead of Merck's pure cholesterol, I used a preparation obtained from gallstones by extraction with ether in the Soxhlet apparatus. For the separation of all saponifiable substances from this ether extract, a method was employed which is based largely on Kumagawa and Sutro.<sup>2</sup> Five grams of the dried ether extract are dissolved in 350 to 400 c c of petroleum ether, to this, 70 c c of a 1 per cent absolute alcoholic solution of potassium hydroxid and 30 c c of distilled water are added. The mixture is shaken and the ether solution of cholesterol separated from the alcoholic solution of soaps in the separating funnel. The petroleum ether is evaporated and the dry cholesterol treated in the same manner a second and, if necessary, a third time. It is finally recrystallized with alcohol. The melting point of this preparation was between 146 and 147 C (294.8 and 296.6 F).

In order to make a watery colloidal emulsion from this crystalline substance by the method of Porges and Neubauer<sup>3</sup> cholesterol is dissolved in acetone and added in small amounts to large quantities of distilled water while stirring. The acetone is evaporated and another portion of the acetone solution is added, the acetone evaporated, and so on, until all the cholesterol necessary for the desired strength has been used. The emulsion is finally filtered through an asbestos filter. When large quantities of this preparation and rather high concentra-

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1 Dewey and Nuzum. The Effect of Cholesterol on Phagocytosis, *Jour Infect Dis*, 1914, xv, 472.

2 Kumagawa and Sutro. Bestimmung des Cholesterins nebst den anderen unverseifbaren Substanzen, *Biochem Ztschr*, 1908, viii, 315.

3 Porges and Neubauer. Physikalisch chemische Untersuchungen über das Lecithin und Cholesterin, *Biochem Ztschr*, 1907, vii, 152.



tions are needed, as for example in these experiments, this method is not ideal, as it consumes an enormous amount of time. The chief difficulty was in getting all of the cholesterol into the state of a fine emulsion, some of it frequently floated on top as "foam." The observation, however, that this so-called foam when taken up with fresh acetone will easily and quickly go into the emulsion, *whether or not acetone is still present*, led to the modification of the method<sup>4</sup>. To a concentrated solution of cholesterol in acetone, warm distilled water is added slowly until the acetone solution, when heated, does not turn clear again. Enough acetone is added to redissolve the precipitate. The clear solution is then slowly poured into warm distilled water. If some of the cholesterol foams out, it is taken up with acetone and added to the emulsion. It is then boiled in small quantities and filtered through an ordinary fine filter paper, using a fresh paper for every new portion. The total is reduced to the desired strength by vacuum distillation and the emulsion finally refiltered.

The making of such an emulsion is time consuming, but, when once made, it is an exceedingly satisfactory preparation. Its chief virtue is its great stability. Such emulsions have been kept for three months and longer without undergoing any apparent change. Heat does not affect them, they can be sterilized in the autoclave repeatedly. They were tested by adding serum and fresh blood from normal and cholesterolized rabbits as well as physiological salt solution. By none of these fluids was the cholesterol precipitated out from its colloidal state. Whatever the ultimate fate of the colloid cholesterol in the blood, it is evidently carried off by the blood stream from the place of the injection without leaving any deposits there. It was thus possible, for example, to make thirty injections in daily succession into the veins of the ears of one rabbit. After intraperitoneal injections, cholesterol deposits in small nodules were generally found on the mesentery, liver, spleen and the under surface of the diaphragm.

The experiment consisted of intraperitoneal or intravenous injections of emulsions of cholesterol into twelve rabbits. Control animals received injections of distilled water from which the added acetone was evaporated.

It seemed proper to assume that the finer the state of division of the colloid cholesterol in the emulsion the better would be the rate and degree of absorption. To test this, three rabbits were injected intraperitoneally with emulsions which had not been filtered, and which ranged between 2 and 5 per cent in concentration. Two of them received seven injections of respectively 20 cc and 10 cc and were killed eleven days after the first injection. The third animal was

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<sup>4</sup> Dewey, Kaethe. The Preparation of Colloidal Emulsions of Cholesterol, Tr. Chicago Path. Soc., 1915, ix, 321.

injected once with 10 c c of a 5 per cent emulsion and was killed five days later. The first two animals had lost in weight at the end of the experiment. The postmortem examination showed that some of the cholesterol had not been absorbed, it was deposited in small nodules, 2 and 4 mm in diameter, chiefly on the liver, spleen and under surface of the diaphragm. The microscopic examination gave convincing evidences that such emulsions are violent in their effect on the tissue, especially on that of the liver. In all three rabbits lesions were found in this organ which have something of the character of an infarct or sequestrum, they are sharply demarcated areas of sometimes considerable dimensions showing marked destruction of the liver structure and enormous deposits of cholesterol in the center, surrounded by a zone of rarified tissue and an outer zone of dense round-cell infiltration. Undoubtedly these deleterious effects of the colloidal cholesterol are due to physical properties, that is, to the presence of large droplets and so-called foam and to the high concentration. Such lesions were not produced by finely filtered emulsions of low or moderate strength, which were employed in all subsequent experiments. Only in one rabbit with previously existing senile changes were similar foci found in the liver; they were, however, few in number and small in dimensions.

Three rabbits were injected intraperitoneally with doses of 10 c c of a 2 per cent emulsion, two of them three times a week for a period of three and five months and the third every day for two months. The first two animals showed a gain in weight at the end of the experiment, the third rabbit lost in weight and was somewhat dull during the last two weeks.

Two rabbits of another group were injected intravenously, one with 5 c c of a 1 per cent emulsion three times a week until sixteen injections were given, the other with a daily injection for thirty days, the first ten doses being 5 c c, the last twenty doses 10 c c of a 1 per cent emulsion. Both remained well during the entire period and gained in weight.

One rabbit received in daily succession thirteen intravenous injections of 10 c c of a 1 per cent emulsion, and ten intraperitoneal injections of 10 c c of a 2 per cent emulsion. It was killed ten days after the last injection. The animal was well until the latter part of the experiment, when there was loss of appetite for several days and loss of weight.

For comparative studies a rabbit was included in the list which showed bowel and urinary disturbances when it was received and which died after four intravenous injections.

Finally, two rabbits were injected intravenously for short periods followed by longer free intervals, at the very end a few intraperi-

toneal injections were given in quick succession. The entire experiment covered 108 days. They gained in weight and only toward the end showed lassitude and loss of appetite.

All animals were killed by air embolism.

Except in the case of the first three rabbits, which were used in a somewhat preliminary experimental way, the serum or whole blood, the bile, and in several instances also the urine, were analyzed for their cholesterol content. The method used was that of Autenrieth and Funk.<sup>5</sup> The chloroform solutions from the various fluids were evaporated down to 5 and 10 cc, 5 cc of these were tested. The reading was done by a Duboscq colorimeter. For histological examination pieces from various organs were fixed in 10 per cent formalin and frozen sections from the kidney, liver, aorta, spleen, adrenal and gallbladder were examined with the polarizing microscope and stained with sudan III. Pieces from various regions of all the kidneys were also prepared for paraffin sections.

In the following tables the histological changes reported are summarized, together with data of the manner, quantity and duration of the injection and figures of serological examinations. They may be helpful in illustrating the extent and the inequality of the effects of cholesterol on various organs of the rabbits. The table of the colorimetric estimation of the cholesterol content of the blood, bile and urine is not complete and, in my opinion, cannot be used as a basis for comparative inferences of any real value. The blood was examined only once that is shortly before the animals were killed. I am therefore not in a position to make any statements regarding the length of time during which the cholesterol injected into the blood is retained therein or in what ratio it is passed through the liver and eliminated with the bile. To all appearances, Weltmann and Biach's<sup>6</sup> belief that a substance, such as cholesterol, which gains access into the blood serum of rabbits, cannot be eliminated, is not confirmed through my experiments. If it were so, the cholesterol content of the blood should be very much higher at any rate in those rabbits which were injected intravenously.

There is one constant factor in the figures of the table which is of interest because of contradictory statements concerning this in literature. In all rabbits, normal, control and cholesterolized, the cholesterol content of the serum is decidedly less than that of the

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5 Autenrieth and Funk. Ueber kolorimetrische Bestimmungsmethoden. Die Bestimmung des Gesamtcholesterins im Blut und in Organen, Munchen med Wchnschr, 1913, ix, 1243.

6 Weltmann and Biach. Zur Frage der experimentellen Cholesteatose, Ztschr f exper Path u Ther, 1913, xiv, 367.

whole blood Some authors hold the view that it is immaterial whether one or the other is used for quantitative estimation of the cholesterol content of the blood, because this is nearly the same in both fluids My observation to the contrary agrees with the results of Abderhalden's<sup>7</sup> investigations of the relative quantities of cholesterol, as well as all the other constituents of the blood, in serum, whole blood and blood corpuscles

From the results in rabbits of the experimentally produced hypercholesterolemia, I venture to draw the following conclusions

- 1 Very small quantities of cholesterol administered by intravenous injections, and relatively small amounts injected intraperitoneally, are sufficient to produce pathologic conditions in some organs of the rabbit

- 2 In intermittent hypercholesterolemia, such as is produced by periodical intravenous injections of small doses, the extent of the cholesterol infiltration and other pathological conditions are entirely out of proportion to the amount of cholesterol injected

- 3 Unfiltered emulsions, that is, those in which the colloid particles are heterogeneous in size, and emulsions of high concentration, have a violent destructive effect on the structures of the liver

- 4 Cholesterol deposits in cells other than those normally and physiologically rich in this lipid substance are not a simple infiltration, but constitute an injury to the function of the cells and signify degenerative processes

- 5 Pregnancy seems to furnish conditions which favor the infiltration of certain organs with cholesterol, from whatever source this may be derived Rabbit 11, which received only 2 gm cholesterol in 108 days by the intermittent method, and which was pregnant twice during this time, had, of all the animals, the most marked cholesterol infiltration and other pathologic conditions in the liver and kidney

The liver of rabbits responds very readily with infiltrative processes to experimental hypercholesterolemia This quick reaction is probably not quite analogous to anything occurring in the human liver, owing to the difference in the effect of hypercholesterolemia in herbivora and carnivora According to Weltmann and Biach the normal elimination of cholesterol through the bile is very slight in the former but increases markedly when they are fed with this substance and the liver stores it up in large quantities In carnivora on the other hand the normal cholesterol content of the bile is high, and doubly refractive substances are not found in the liver of the dog, the cat and the white rat, even when fed with very large quantities of food rich in

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<sup>7</sup> Abderhalden *Lehrbuch der physiologischen Chemie*, Berlin, 1906, p 592

TABLE 1—CHOLESTIROL CONTENT OF BODY FLUIDS AND VARIOUS—

Number and Sex of animals	Weight in Gm		Kind, Periodicity and Total Number of Injections	Quantity and Concentration of Single Dose	Total Amount of Cholesterol Injected, Gm	Duration of Experiment, Days	Quantitative Estimation of Cholesterol in Gm			
	Beginning	End					Serum	Whole Blood	Bile	Urine
I Male	1,970	1,840	Intraperitoneal 1	20 c c 2 to 5% unfiltered emulsions	4 in 9 days	11	*	*	*	*
II Male	1,920	1,750	Intraperitoneal 1	10 c c 2 to 5% unfiltered emulsions	2 in 9 days	11	*	*	*	*
III Female	1,890	1,880	Intraperitoneal 1	10 c c 5% unfiltered emulsions	0.5	5	*	*	*	*
IV Male	1,540	1,700	Intraperitoneal 3 times a week 40	10 c c 2%	8	98	0.054	0.200	0.121	Not collected
V Female	1,690	1,770	Intraperitoneal 3 times a week 52	10 c c 2%	12.4	155	0.066	0.109	0.195	0.026
VI Female	2,200	1,960	Intraperitoneal every day 58	10 c c 5%	11.6	60	0.095	0.107	Numerous gallstones	Not enough obtained
VII Female	2,180	2,520	Intravenous 3 times a week 16	5 c c 1%	1	36	0.066	0.183	0.200	Not enough obtained
le	1,970	2,130	Intravenous every day 30	10 injections 5 c c, 20 injections 10 c c 1%	2.5	32		0.179	0.174	0.015
IX Male	1,970	1,790	13 intravenous, 10 intraperitoneal every day	Intravenously 10 c c 1% intraperitoneally 10 c c 2%	3 in 23 days	33		0.320	Numerous small concretions	0.010
X Male (sick)	2,290	2,110	Intravenous every day 4	5 c c 1%	0.2	4	†		0.041	Negative
XI Female	1,750	2,100	Intravenous by intermittent method 27	5 c c 1%	2 in 98 days	108	†			
XII Male	1,790	1,850	Intravenous by intermittent method 27	5 c c 1%	2.4 in 98 days	108		0.291	Numerous small concretions	0.014

\* Not examined

† Died

—ORGANS OF RABBITS INJECTED WITH EMULSIONS OF CHOLESTEROL

Liver	Gallbladder	Aorta	Adrenal	Spleen	Kidney
Marked infiltration and foci of tissue destruction with cholesterol deposits Proliferation of connective tissue		Small amounts of cholesterol and fat	Enormous amounts of cholesterol	Small amount of doubly refractive substances	Small amount of cholesterol No degenerative processes
Marked infiltration and foci of tissue destruction with cholesterol deposits Proliferation of connective tissue		Cholesterol and fat in entire intima, which is not thickened	Fair amount of cholesterol	Negative	Small amount of cholesterol Very degenerative
Infiltration and foci of tissue destruction as in I and II, but on a small scale		Negative	Fair amount of cholesterol	Negative	Limited amount of cholesterol in tubules degenerative processes
Moderate amount of diffuse cholesterol infiltration in peripheral portion of lobules	Negative	Small amount of cholesterol and fat in media and intima	Fair amount of cholesterol	Scanty amount of doubly refractive substances	Small amount of cholesterol Very degenerative processes
Enormous amount of diffuse cholesterol infiltration Marked proliferation of connective tissue	A few small concretions	Small amount of cholesterol and fat in media	Fair amount of cholesterol	Fair amount of doubly refractive substances	Considerable amount of cholesterol Very degenerative
Almost complete absence of cholesterol	Filled with small and larger gall stones	Negative	Moderate amount of cholesterol	Scanty amount of doubly refractive substances	Considerable amount of cholesterol Very degenerative
Moderate amount of cholesterol infiltration and small foci of tissue destruction with cholesterol deposits	Negative	Marked fatty degeneration and calcification of media (spontaneous)	Large amount in one very scanty in other	Scanty amount of doubly refractive substances	Small amount of cholesterol Very degenerative
Moderate amount of cholesterol infiltration Proliferation of connective tissue	Negative	Small amounts of cholesterol deposits in thickened intima	Considerable amount	Negative	Moderate amount of cholesterol Very degenerative
Considerable amount of diffuse cholesterol infiltration Slight proliferation of connective tissue	Numerous small concretions	Small amounts of cholesterol in intima	Abundance in one, scanty amount in other	Negative	Fair amount of cholesterol Very degenerative
Moderate amount of cholesterol infiltration	Negative	Negative	Moderate amount of cholesterol	Negative	Very limited amount of cholesterol Very degenerative
Enormous amount of diffuse cholesterol infiltration Marked proliferation of connective tissue	Negative	Moderate amount of cholesterol and fat in media and intima	Small amount of cholesterol	Very scanty amount of doubly refractive substances	Very extensive amount of cholesterol Very degenerative
Considerable amount of diffuse cholesterol infiltration	Numerous small concretions	Negative	Small amount of cholesterol	Scanty amount of doubly refractive substances	Fair amount of cholesterol Very degenerative

cholesterol (Bacmeister and Havers,<sup>8</sup> Weltmann,<sup>9</sup> Chatalow,<sup>10</sup> Anitschkow and Chatalow<sup>11</sup>) In the omnivorous pig and in man the elimination of cholesterol by the bile is even greater than in carnivora The liver is therefore able to adjust itself in man and in carnivora to great oscillations in the cholesterol content of the blood, whereas in herbivora, "insufficiency" on the part of this organ is, to a certain degree, physiologic (Weltmann<sup>9</sup>), hence the ready infiltration of the liver of rabbits in experimental cholesterolemia

In the rabbits of my experiment this infiltration presents several peculiarities Apparently the amount is not proportionate to the quantity of cholesterol injected, nor directly dependent on the mode of the injection The most extensive infiltration was found in Rabbit

TABLE 2—CHOLESTEROL CONTENT OF BODY FLUIDS IN NORMAL AND CONTROL RABBITS

Number of Animal			Injections of Control Rabbits	Quantitative Estimation of Cholesterol in Gm			
				Serum	Whole Blood	Bile	Urine
XIII	Male	Normal		0.080	0.137	Trace	Negative
XVI	Male	Normal		0.080	0.121	Trace	Negative
XV	Male	Control	Intraperitoneal, every day, 24 injections	0.074	0.088	0.014	Negative
XVI	Male	Control	Intraperitoneal 3 times a week for 4 months	0.080	0.106	0.024	Negative
XVII	Female	Control	Intravenous 3 times a day, 43 days	0.072	0.130	0.038	Negative

11, which received the smallest amount of cholesterol as measured by the length of time in which it was given In the animal similarly treated, Rabbit 12, it was very much less Rabbit 6, which received the large quantity, 11.6 gm of cholesterol within two months, was quite exceptional in that doubly refractive substances were almost entirely absent in the liver, while the gallbladder was filled with gallstones Rabbit 5, having received 12.4 gm cholesterol in five months

8 Bacmeister and Havers. Zur Physiologie und Pathologie des Cholesterinstoffwechsels, Deutsch med Wchnschr 1914, \1, 385

9 Weltmann. Zur klinischen Bedeutung des Cholesterinnachweises im Blutserum, Wien klin Wchnschr, 1913, \XVI, 874

10 Chatalow. Ueber experimentelle Cholesterin-Lebercirrhose in Verbindung mit eigenen neuen Erhebungen über flüssige Kristalle des Organismus und über den Umbau der Leber, Zieglers, Beiträge, 1913, lvi, 85

11 Anitschkow and Chatalow. Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, Centralbl f allg Path u path Anat 1913, \XIV 1

by the same kind of injection, showed enormous amounts of tropic substances in the liver, and only a few sandy concretions bile. Two of the control animals had some cholesterol deposited in the liver. There is no uniformity in the distribution or in the type of the infiltration with cholesterol. In a few instances it is disseminated all through the lobules, in some it is located chiefly in the peripheral portion and densest nearest the periportal spaces. In general, it occurs predominantly in disseminated areas of various dimensions. These are always limited strictly to the lobules, but within the lobules they are scattered very arbitrarily, as it seems. The cholesterol ac-



Fig 1—Doubly refractive substances from the liver of Rabbit 11, received 2 gm cholesterol by the intermittent method in 108 days. Pic

lation in such areas is very marked, in the intervening portions there is none. A discriminative involvement of the liver cells or the endothelial cells cannot be observed. There is, too, an obvious radiate arrangement of the deposits (see Fig 1), the cholesterol droplets being sometimes chiefly intralobular, sometimes chiefly in the columns of liver cells. Quite often both kinds of cells are equally involved, this is especially the case when these dense cholesterol accumulations are of large dimensions. Almost without exception the connective tissue spaces are free from cholesterol, neutral fat, however, when present, is a



found in this location. The prevalent occurrence of disseminated cholesterol deposits was not observed until the gallbladders of the rabbits were examined. On this occasion the presence of cholesterol in portions of the liver adjacent to the gallbladder in Control Rabbit 14 was discovered. In previously examined portions of the liver no doubly refractive substances had been found.

There was one type of cholesterol deposits which seemed at first limited to one group of rabbits, that is, those injected intraperitoneally with unfiltered emulsions of high concentration, but eventually identical foci, although smaller in size, were found in Rabbit 7 which had been injected intravenously with small quantities of well-filtered emulsions of 1 per cent strength the total amount of cholesterol being only 1 gm in thirty-six days (see Fig 2). These were well-demarcated areas of destruction of the liver parenchyma with large deposits of a reddish yellow material not all of which appeared as doubly refractive substances under the polarizing microscope. The cholesterol esters were probably not simply liberated from their cell boundaries in the process of disintegration, but were broken up and new cholesterol compounds were formed which have no anisotropic properties. Since all the animals of Group 1 had such lesions and, with the one exception mentioned, none of the others, we may assume that the large quantity of cholesterol in a dose, the high concentration, and possibly the presence of large particles in the emulsion, were responsible for the destructive effect. Cells, probably perfectly normal until the time of the first injection, were suddenly taxed far beyond their capacity of intake and output, no time being given them for adaptation to an abnormal task, they succumbed completely. Rabbit 7, in which the cholesterol was gradually introduced in fine homogeneous emulsions of low strength and in small doses (1 gm in thirty-two days), the conditions which made similar lesions possible are in all likelihood the following: (a) The rabbit was old, if we judge from the presence of the marked spontaneous arteriosclerotic processes of the aorta, (b) the liver had undergone senile changes, as shown by frozen sections not treated with alcohol, (c) the capacity of the liver cells for the taking up and giving off of an excess of cholesterol was much below par, and they succumbed under a proportionately small task and in spite of the time given them for adaptation.

Chatalow<sup>10</sup> attributes the injurious effect of cholesterol on the cells not to its chemical, but to its physical properties. This substance is deposited in the organs in the form of liquid crystals, as these anisotropic droplets become larger by confluence of smaller ones, and accumulate in sufficient numbers, they act as foreign bodies. But how are we to account for the accumulation of cholesterol esters in spots? Apparently only some Kupffer cells, sometimes in widely sepa-

rated regions, take up an excess of cholesterol from the blood and cause the neighboring liver cells to be loaded with anisotropic substances. The typical cholesterol infiltration seems to be focal and not diffuse, as illustrated in the liver by the disseminated areas of dense cholesterol accumulations and the focal regions of necrosis. It suggests an elective action on the part of the endothelial cells, whose normally phagocytic action is here coupled with the function of conveying their charge to other cells, that is, the liver cells.

Since to all appearances the amount of cholesterol infiltration in the liver as well as in the kidney sometimes is entirely out of propor-

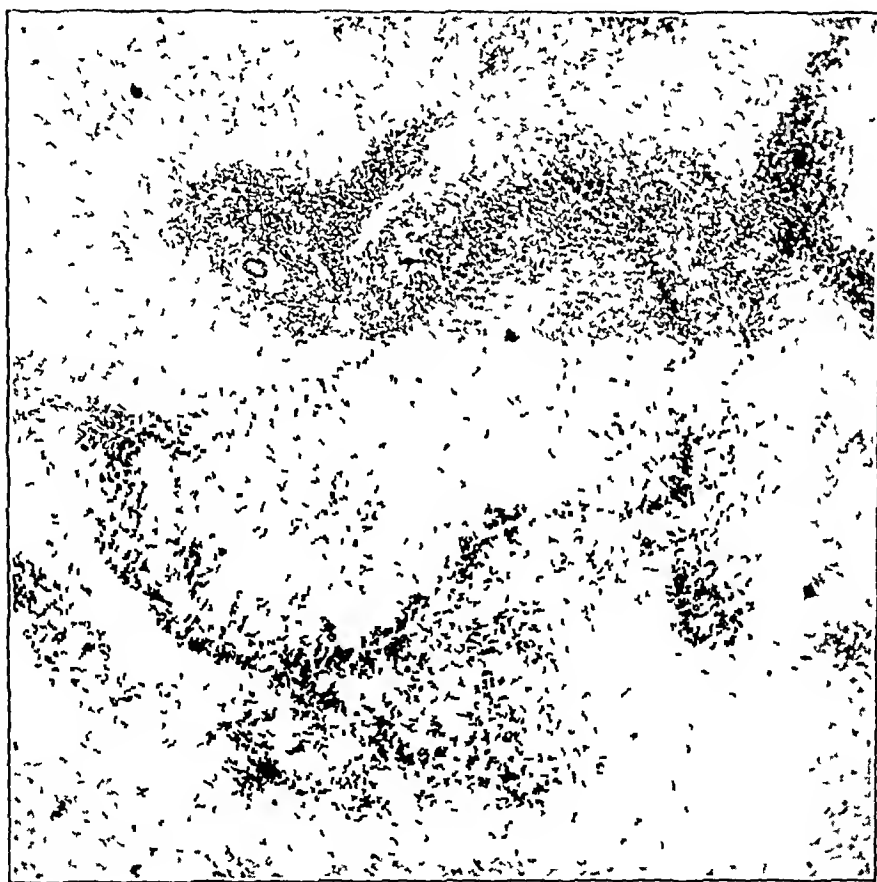


Fig 2—View of liver substance stained with sudan III and hematoxylin. Large focus of tissue destruction, with large amounts of cholesterol deposits, from Rabbit 1, which received intraperitoneally 4 gm cholesterol in unfiltered emulsions of high concentration.

tion to the quantity injected, a considerable portion of it must be regarded as spontaneously produced. It may be assumed that the initial infiltration which follows the first suddenly established period of hypercholesterolemia renders the cells more susceptible to later periods and even reduces their capacity for the normal amount of work in the cholesterol metabolism. This again constitutes a factor in a general disturbance of the cholesterol regulating machinery. It has

been said that the cholesterol content of the blood is very easily changed so that even the suspending of the animal for bloodtaking produces variations in the figures. With such premises we may easily believe that the constantly repeated irritation from intraperitoneal injections for four months in a control rabbit caused a periodical occurrence of spontaneous hypercholesterolemia, followed finally by an infiltration of an organ which normally is chiefly concerned in the cholesterol metabolism, but which in the rabbit becomes readily "insufficient."

In pregnancy hypercholesterolemia occurs physiologically (Sternberg,<sup>12</sup> Huffmann<sup>13</sup>). But there is no parallel increase in the elimination of cholesterol through the bile. Bacmeister and Havers<sup>8</sup> attribute this hypercholesterolemia to retention of the lipoids and not to endogenous new formation in the body. Toward the end of pregnancy, the "liver filter" becomes denser and the liver cells shut off the outflow of the blood cholesterol into the bile. These authors admit, however, that there may be also an alteration in the constitution of the lipoids themselves, as a result of which the chemically changed cholesterol compounds cannot pass through the unchanged liver cells. A normal pregnant rabbit which I examined showed no trace of anisotropic substances in sections from various portions of the liver, but I found a fair amount of cholesterol in that of the pregnant Control Rabbit 13, which received sixteen intravenous injections of the control fluid (free from cholesterol) and was under observation for forty-three days. A pus infection in the external meatus which had been present was discovered only when the badly involved ear was to be used. It was also bitten in the ear by another rabbit and had to be isolated. It is reasonable to assume that the repeated irritation from intravenous injections, the treating of a painful ear and even the frequent examination of the rectal temperature contributed toward further increasing the physiological hypercholesterolemia of pregnancy with subsequent cholesterol infiltration in the liver. Rabbit 11, which was injected intravenously by the intermittent method and received only 2 gm. in one hundred and eight days, had, of all the animals, the most marked cholesterol infiltration of the liver and the kidney. It was pregnant twice during this period and in that condition at the time of death. There is no doubt that a large part of the amount of cholesterol in the organs of this rabbit was not that retained from the injections but was spontaneously produced. We have here an example, I believe, of a case in which hypercholesterolemia and cholesteatosis may be the cause and effect.

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12 Sternberg Die Nebenniere bei physiologischer (Schwangerschaft) und artifizierter Hypercholesterinämie, Beitr. z. path. Anat. u. z. allg. Path., 1914, 1x, 91.

13 Huffmann Zur Bestimmung des Gesamtcholesterins im Blute an geburts-hilflichen und gynäkologischen Fällen, Zentralbl. f. Gynäk., 1915, xix, 33.

of pathologic conditions. The primary cause of both may be disturbed cellular functions of momentary, short or long duration, thereby changing the lipid character of the cell. Food as such probably plays a very small part, if any, in the production of cholesterol deposits in functioning organs.

An interesting coincidence is the lack of any noteworthy cholesterol infiltration of the liver and the presence of numerous gallstones in the gallbladder of Rabbit 6 which was injected intraperitoneally each day for two months with 10 c.c. of a 2 per cent emulsion. The kidney showed as much cholesterol infiltration as in other marked cases. The

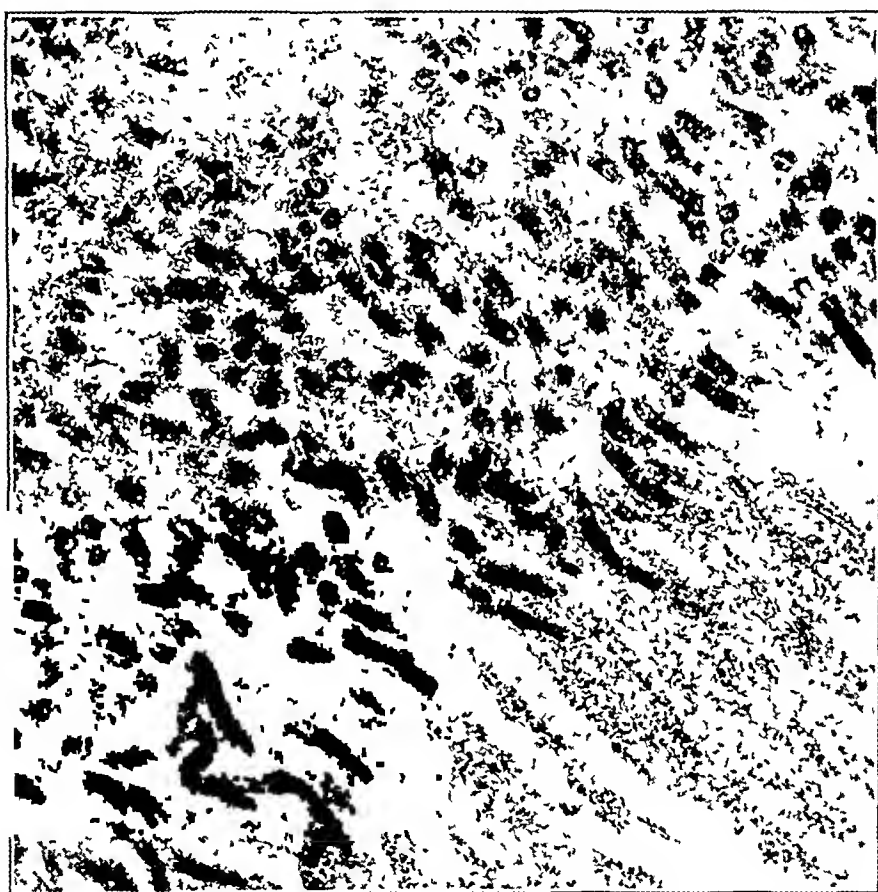


Fig. 3—View of kidney tissue stained with sudan III. Marked infiltration of tubules with cholesterol, from Rabbit 11.

cells of this liver were apparently unusually permeable and capable of taking up and giving off large quantities of cholesterol without loading themselves with anisotropic substances. It was an exceptionally well functioning filter and in this respect more comparable to the liver of carnivora, but on account of the unhindered passage of enormous quantities of cholesterol through the rabbit's liver, there was a constant abnormally high cholesterol content of the bile and gallstones formed. In two other rabbits, which had numerous sandy concretions, the infil-

tration of the liver was considerable, although not excessive, and was of the diffuse type involving chiefly the Kupffer and endothelial cells

The results of my experiments differ in some respects from those of Chatalow<sup>10</sup> These differences arise, of course, from the methods employed In his case considerable quantities of fat were given with cholesterol and consequently large amounts of fat reappeared in the liver In my experiments no fat and no other lipoids besides cholesterol were given, and in no instance does fat appear in the liver structure, where it does occur, it is limited to the periportal spaces widened by proliferation of connective tissue Chatalow's explanation of the manner in which the anisotropic infiltration or "Verfettung" may occur is not applicable to my observations He states that "it is necessary that isotropic fats accumulate in sufficient quantity in the organ and perhaps also that free fatty acids develop, in order that cholesterol may be bound and retained" According to him, deposits of anisotropic fats are observed chiefly in those portions of the liver in which the isotropic fats are concentrated, and consequently also saturated with cholesterol compounds Chatalow himself admits that in his explanation he considers exclusively his experiments of feeding animals with cholesterol dissolved in sunflower seed oil That in some pathologic conditions of the human liver the increase of the fatty constituents may be associated with an increase of its cholesterol content and with a corresponding rise in the cholesterol content of the bile, appears from the work of Le Count and Long<sup>11</sup> I also failed to find proliferation of the epithelium of the bile ducts or hypertrophic proliferation of these ducts such as Chatalow describes Anisotropic substances were not found in the epithelium of these ducts or in that of the gallbladder, and only rarely a substance which takes the cholesterol tint with sudan III was seen in the epithelial cells of the smaller bile ducts Chatalow states that the oil of sunflower seed does not produce any pathologic alterations in the liver, that it appears very soon in the epithelial cells of the bile ducts and in the liver cells surrounding the central vein, and that it is eliminated with the bile, passes over into the blood, and in continued feeding produces a diffuse, even infiltration in the liver He believes that the presence of fat in the epithelial cells favors the increased elimination of cholesterol compounds and that the irritation from these incites the proliferation of connective tissue Finally a substitution of true liver cells by proliferated cells of the bile ducts, as he observed could not be demonstrated in the livers of my rabbits Whenever the infiltration with cholesterol was diffuse and located in the peripheral portion of the lobule, the cells thus infiltrated reached

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14 LeCount and Long The Relation Between the Fat Content of the Bile and Fatty Changes in the Liver, *Jour Exper Med*, 1914, *xx*, 234

to the very border line, while the newly formed cells observed by Chatalow, although morphologically like true liver cells, did not functionate as such, that is, they did not take up cholesterol. In closer analogy with my findings are the observations of Rothschild,<sup>15</sup> who studied the relations of hypercholesterolemia in rabbits following bilateral suprarenectomy, and the increase of the amount of cholesterol in the liver and in the bile. Deposits of anisotropic substances were found



Fig 4—View from the same kidney as Figure 3. Paraffin section stained with hematoxylin and eosin. Triangular area with the base toward the capsule showing marked degenerative processes.

only in Kupffer cells. The epithelial cells of the bile ducts were free from cholesterol, and those of the gallbladder only occasionally contained single isotropic fat droplets. According to Rothschild the Kupffer cells are the intermediary and the liver the "regulating" organ

<sup>15</sup> Rothschild. Ueber die Beziehungen der Leber zum Cholesterinstoffwechsel, Beitr z path Anat u z allg Path, 1914, 1x, 66

in the cholesterol metabolism, inasmuch as it maintains the cholesterol equilibrium of the organism through the elimination in the bile

The sources of the cholesterol in spontaneous hypercholesterolemia, physiological and pathological, are yet unknown. They are probably manifold, including physical and chemical alterations of the cell as well as functional disturbance of entire organs. The various parts of an intricate cholesterol metabolic apparatus may be in such intimate interaction that insufficiency on the part of one will throw an extra burden on another engaged in a different manner in the cholesterol work, which again involves another, producing a state of functional instability. Some organs seem to be preeminently depots, such as the adrenals, the ovaries,<sup>16</sup> the fatty tissue, from which the cholesterol is mobilized, so to speak, in time of general disturbance. Rothschild<sup>16</sup> showed that in a state of inanition rabbits present a condition similar to that following suprarenectomy, namely, an increase of cholesterol in the blood, the adrenal, the liver and the bile. He believes that the increase of this substance in some of the vital organs may be attributed to an increase of the blood cholesterol, and this again to a greater activity in the catabolic cellular processes, chiefly in the less vital organs (fatty tissue). The great variations in the effect of cholesterol on the liver of the rabbits in my experiments indicate a great variability in the functional adaptability of the liver cells to the increased influx of cholesterol from the blood. Such differences may arise from age, sex, disposition, that is, individual tendencies, transitory or lasting morbid conditions. Cholesterol alone in excessive quantities may have a destructive effect on normal, healthy cells and injure them beyond the possibility of recuperation. Continued overtaxing of the cells from long-sustained hypercholesterolemia may cause "insufficiency" with ultimate destruction of parenchyma. Individually, the normal function may be below the average requirements and this relative insufficiency may cause deposits in other organs, but the cells, primarily weakened and impaired, succumb readily even to a slight increase of the blood cholesterol. This primary alteration itself may be an alteration of the lipid character of the cell. According to Chvostek,<sup>17</sup> the infiltration of an organ with cholesterol is preceded by an alteration in the constitution of the cells (cutaneous), as a result of which the lipid substances already existing in the cells, are separated from their combinations and made visible, and the introduction of fresh cholesterol causes an infiltration of such cells with this substance.

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16 Rothschild. Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, Beitr. z. path. Anat. u. z. allg. Path., 1915, 1x, 227.

17 Quoted from Weltmann and Biach (Note 6).

The mucosa of the gallbladder examined by the polarizing microscope was absolutely free from doubly refractive substances in all rabbits. In histological sections three of them, Rabbits 6, 8 and 9, presented an exceptional feature. A substance which stains reddish with sudan III and purplish blue with Nile blue sulphate is present abundantly in a number of villi. It is not in the epithelium, for this is shed, but it generally occupies the central portion of the villus, forming designs which recall the chyle ducts in the intestine. They are often branched or spider like and are probably widely distended lymph channels filled with fat and such cholesterol compounds as have no anisotropic properties (see Fig 5). In the finer branches particularly



Fig 5—Gallbladder, stained with sudan III and hematoxylin. Widely distended lymph vessels in the mucosa filled with cholesterol and fat, from Rabbit 8, which received intravenously 25 gm cholesterol in thirty-two days.

it is clearly seen that rather large cells, which occupy these vessels, are loaded with granular reddish stained material. Kaufmann<sup>18</sup> mentions such observations with regard to the human gallbladder, the substance, which is within large cells in lymph vessels, is fat, and he believes that it is resorbed from the bile. Lichtwitz<sup>19</sup> describes masses

<sup>18</sup> Kaufmann. Lehrbuch der speziellen pathologischen Anatomie, Berlin, 1911 (1), p. 622.

<sup>19</sup> Lichtwitz. Ueber die Bildung der Harn- und Gallensteine, Berlin, 1914, p. 69.



lying beneath the epithelium in a human gallbladder, which were doubly refractive substances. He states that in some places they had broken through the mucosa. A relation to the lymph vessels could not be observed. From the picture he concludes that the masses containing cholesterol penetrate from the gallbladder to the surface of the mucosa, thence into the bile. According to him the bile receives its cholesterol from two sources, from the liver cells and from the gallbladder wall. He writes: "Since the solubility of cholesterol is achieved by means of other colloidal substances, it is quite possible that the condition of the solution varies with the source of the cholesterol." The "liver cholesterol" may have a solubility different from that of the "wall cholesterol." In this interpretation he disagrees with Aschoff and Bacmeister<sup>21</sup> who believe that the cholesterol of the gallbladder wall has been resorbed from the bile as esters and set free in the epithelium of the bladder. The diverging views about the origin of the biliary cholesterol are represented on the one side by Chauffard, Laroche and Grigaut,<sup>1</sup> and Naunyn<sup>22</sup> who consider it as a secretion of the epithelial cells of the bile ducts, and on the other side by Aschoff,<sup>23</sup> Landau and McNee<sup>24</sup> and Rothschild.<sup>15</sup> According to these authors, cholesterol found in the epithelium of the gallbladder is a result of resorption from the bile.

In several rabbits the mucosa of the gallbladder showed a very extensive desquamation of the epithelial cells, which for various reasons I am inclined to consider as due not to postmortem changes, but to the irritating intravital action of an excess of cholesterol in the bile. The necropsy was made immediately after killing the animals, and the bile was withdrawn with a pipet. In Rabbit 11, which died unexpectedly and whose necropsy could be made only on the following day, the mucosal lining was preserved. It was intact also in Rabbit 12. These two rabbits received very small quantities of cholesterol by the intermittent method during a period of 108 days. From the extensive cholesterol infiltration in the liver we may presume that the elimination of cholesterol through the bile was not abnormally increased. In all those rabbits which had gallstones or small concretions, besides some which had none, but whose bile probably had an excess of cholesterol, the desquamation of epithelial cells was very marked. The shed cells

20 Quoted from Lichtwitz (Note 19)

21 Chauffard, Laroche and Grigaut. Sur l'origine de la cholestérine biliaire. Recherches expérimentales sur la cholestérimie après ligature du choledoque, Soc. biol., 1913, lxxiv, 1005 and 1093.

22 Naunyn. Quoted from Lichtwitz (Note 19)

23 Aschoff. Zur Frage der Cholesterinbildung in der Gallenblase, München med. Wchnschr., 1906, lxx, 1846.

24 McNee. Zur Physiologie des Cholesterinstoffwechsels, Beitr. z. path. Anat. u. z. allg. Path., 1914, lvi, 667.

retained in the lumen in paraffin sections, showed all stages of disintegration. The denuded villi were sometimes matted together forming a network in the meshes of which there were cell debris and pigment.

Gallstones of any appreciable size produced by experimental hypercholesterolemia have not been reported previously in literature. The contracted and knotty gallbladder of Rabbit 6 contained a number of small concretions and twelve stones with a diameter of 2 and 3 mm, the small amount of bile which could be withdrawn was full of black granules. The gallstones were irregular, brittle and not faceted. Some of them were treated and embedded in paraffin by the method of Aoyama<sup>25</sup>. Sections stained with methylene blue showed that disintegrated cells formed the framework of these stones, while cell remnants and faint nuclei were still discernible in the outer portion of such sections. The cell debris was rolled up and held together with pigment and calcareous substances and the masses thus formed were placed tile-like in apposition forming parallel trabeculae. Bacteria were not found in the gallstones, in the lumen or in the gallbladder wall. All indications of inflammatory processes also were lacking. Evidently these gallstones were formed in sterile bile. The liver of this rabbit did not show any noteworthy cholesterol infiltration in sections taken from five different portions. The greatly hypercholesterolemic blood passed through this exceptionally permeable organ unimpeded and enormous quantities of cholesterol were poured out into the bile, which acted as a violent irritant on the epithelial cells, they were injured and desquamated en masse, clumped together and formed the organic scaffold to which the substances precipitated from the bile were anchored. These multiple stones of trabecular construction with a clearly organic scaffold, of recent formation and of a noninflammatory origin I do not venture to identify with types of human gallstones. The differences in the normal conditions in rabbits from those in man suggest equal differences in pathologic processes. It is known that human gallstones not soluble in human bile may dissolve in animal bile. Aschoff<sup>26</sup> pointed out that not only is the cholesterol content of the bile in the dog, the rabbit and the ox strikingly small as compared with that in man, but there are also differences in the relative values of the other constituents, all of which result in a difference of solubility.

The chief analogy of value between these experimentally produced gallstones and those occurring in man lies in the association of gallstone formation with hypercholesterolemia. The frequent occurrence of gallstones in women has often been attributed to mechanical factors,

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25 Aoyama. Zur Frage der Cholelithiasis, Beitr. z. path. Anat. u. z. allg. Path., 1913, LVII, 169.

26 Aschoff. Wie entstehen die reinen Cholesterinsteine? Munchen. med. Wchenschr., 1913, LX, 1753.

among them pressure effects in pregnancy. Hypercholesterolemia is always associated with this condition, and probably plays the greater part. Herrmann and Neumann<sup>27</sup> believe that the high cholesterol content of the blood in pregnancy is the result of retention in the blood, in the puerperium most of it is eliminated by the milk, nonlactating women retain the lipoidemia longer. Aschoff,<sup>28</sup> however, states that only part of the blood cholesterol is carried off by the milk, as also by the urine, another portion is eliminated through the bile, as some observations of McNee<sup>29</sup> indicate. According to Bacmeister and Havers,<sup>3</sup> the greater density of the liver during the latter part of pregnancy causes retention of the blood cholesterol, and immediately after delivery cholesterol is suddenly poured out in abundance into the bile. Aschoff<sup>28</sup> calls attention to the observation that the first attacks of gallstones are often observed in pregnancy and that we may assume stone formation to occur during or shortly after labor. The structure of these pure cholesterol stones, which are not concentric, but of a chaotic, trabecular type, indicates a more or less hurried formation by the crystallizing out of pure cholesterol from the bile. They are, as a rule, of a non-inflammatory origin, occur at a relatively early age, and are the result of hypercholesterolemia followed by sudden precipitation processes in the bile under the influence of labor or the puerperium.

Compared with the well marked effects of cholesterol in the kidney and liver in most of the rabbits the involvement of the aorta was slight. Macroscopic changes were absent in all but one. As examined by the micropolariscope, cholesterol was entirely absent in three, and the amount was slight in three others. The very marked process of degeneration in the media of Rabbit 7 must be considered as spontaneous, that is, of the adrenalin type referred to in literature, because none of the alterations were found in the aorta of any of the others, all of which, except one, had received much larger doses. Weltmann and Biach<sup>6</sup> state that they failed to produce any atheromatous changes with deposits of doubly refractive substances in the aorta of rabbits fed with cholesterol for some time. By primarily injuring the blood vessels through injections of adrenalin an arteriosclerosis of the adrenalin type occurred in such rabbits. Anisotropic substances, however, were not observed by them. Perhaps much larger quantities of cholesterol by feeding than these authors used and larger amounts than I administered by intraperitoneal and intravenous injections are necessary to

27 Herrmann and Neumann. Ueber die Lipide der Graviditat und deren Ausscheidung nach vollendeter Schwangerschaft, *Wien klin Wchnschr*, 1912, **xxv**, 1557.

28 McNee. Zur Frage des Cholesteringehalts der Galle wahrend der Schwangerschaft, *Deutsch med Wchnschr*, 1913, **xxxix**, 995.

29 Aschoff. Bemerkungen zur Arbeit von McNee, *Deutsch med Wchnschr*, 1913, **xxxix**, 995.

produce such thickening of the intima with large cholesterol deposits as Anitschkow<sup>30</sup> described. In my observation large intima cells were present in nearly all the instances where cells of this layer of the vessel wall were infiltrated with cholesterol, but they were not increased in number, they were simply enlarged intima cells proper, the ballooned protoplasmic body bulging out into the lumen of the vessel. Nodular thickening of the intima occurred in two cases, but it was of the type of hypertrophic connective tissue, in the center of which there were some cholesterol deposits. Fat was generally found in addition to cholesterol and often in greater amount than this. An observation of some interest was the uniform marked infiltration with fat and cholesterol of the entire intima and some adjoining layers of the media in an instance where a tear through the inner layers of the aorta was found (probably agonal or postagonal).

As to the adrenal, it is impossible to systematize the observations. Seemingly there is no correlation between the amount of cholesterol in this organ and that in the liver and kidney as far as these experiments are concerned. As determined by the micropolariscope, it varied sometimes greatly in the two adrenals of the same rabbit. In Rabbit 14, a control animal for intraperitoneal injections, the amount of cholesterol in both adrenals was scanty, in Rabbit 13, control animal for intravenous injections, which was pregnant when killed, there was an abundance. The same was observed in a normal pregnant rabbit Rabbit 11, also pregnant at the time of death, and in which the cholesterol infiltration in the liver and kidney was most marked, had a small amount of cholesterol in the adrenal. In still another control animal in the early stage of pregnancy there was a very scanty amount of doubly refractive substance in the adrenal. There were great variations in the state of division and in the distribution of the crystalline substances. They were finely or very finely divided or occurred in coarse conglomerations. In four cases the glomerulosa was almost entirely free from cholesterol. Fat was present in abundance in all, and apparently more so in proportion as the amount of cholesterol was scanty.

My observation of the amount of doubly refractive substances in the spleen of the cholesterolized rabbits agrees with that of Weltmann and Viach, who found only small quantities of anisotropic droplets in this organ. There was no cholesterol, as determined by the polarizing microscope, in the spleen of four, and a very scanty amount in that of six rabbits. In all it occurred in exceedingly finely divided crystalline substances. But as in the kidney and the gallbladder, so also in

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30 Anitschkow Ueber die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose, Beitr z path Anat u z allg Path, 1913, lvi, 379

the spleen, there may have been cholesterol compounds which were not anisotropic, for in sections stained with sudan III there were often more or less numerous small areas which took the typical cholesterol tint. A striking occurrence of large infiltrated cells, such as described by Amitschkow<sup>31</sup> and by Soper,<sup>32</sup> I was unable to observe.

Weltmann and Biach<sup>6</sup> are the only authors, to my knowledge, who have produced an infiltration of the kidney with cholesterol in rabbits. In addition to feeding them with this substance they injected uranium nitrate and adrenalin in order to favor such an infiltration, which they failed to produce with cholesterol alone. They fed a rabbit for twenty-four days with 1 gm cholesterol daily. During the last seven days of this period uranium nitrate was injected intraperitoneally in three doses. Macroscopically the kidney showed the signs of nephritis. The polarizing microscope revealed doubly refractive substances in the epithelium of the tubules which appeared as "light stripes." "This localization," the authors write "is interesting inasmuch as in nephritis from uranium poisoning an injury to the tubular apparatus is, according to the investigations of Suzuki, the chief involvement." A second experiment, in which the effect of uranium nitrate was combined with that of adrenalin, the kidney showed a similar picture, although less pronounced. A control experiment with pure uranium nitrate without cholesterol had negative results.

The results of the polariscopic examination of the kidneys in my experiments need a special explanation. Doubly refractive droplets, which after heating show the cross figure on cooling, could be demonstrated only in one case, where these substances formed luminous, compact bands of varying length within the lumen of the straight tubules, and formed a narrow lining of some neighboring tubules. Single scattered droplets were seen in many kidneys in considerable number as they were quite generally observed in the spleen. But the substance which infiltrates tubules in foci, and which takes the typical yellowish red tint with sudan III, did not flash up as sparkling doubly refractive droplets under the polarizing microscope. They appeared as tubules with a somewhat dull silvery hue. Their relief against the background with darker tubules was not marked enough to give satisfactory photomicrographs. But so invariably did they reappear in sudan III stained sections that the conviction was very strong that this substance was cholesterol. It would be interesting to know whether Weltmann and Biach's remark that the doubly refractive droplets "als

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31 Amitschkow. Ueber experimentell erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr z path Anat u z allg Path, 1913, 57, 201.

32 Soper. Zur Physiologie des Cholesterinstoffwechsels, VI. Ueber Beziehungen der Milz zum Cholesterinstoffwechsel, Beitr z path Anat u z allg Path, 1915, 1x, 232.

helle Streifen aufleuchteten" would apply to the tubules which I describe as silvery. The kidneys examined had been in formalin for periods of different lengths. The characteristic cross figure could not be observed.

Several explanations for the nature and aspect of these substances are possible. The doubly refractive droplets are advantageously studied when isolated. This is easily done by allowing them to pass with the water beyond the margin of the section, or by squeezing them with slight pressure out of a well-infiltrated section, for example, from a fresh adrenal. It will then be noticed that the droplets are of all sizes and that the black cross is still discernible in extremely minute droplets, so minute that they cease to sparkle, and droplets can be seen so infinitesimal that the cross figure is beyond the limit of vision. There is no reason to believe that in a collection of droplets in which all those large enough to exhibit the cross can be identified as anisotropic droplets the smallest ones are different. Droplets of such extremely small dimensions would hardly flash up with brilliancy, but would rather have a dim appearance under the polarizing microscope. Weltmann and Biach say of the adrenals of normal rabbits, that "they show a fine fog of doubly refractive droplets and relatively few large ones." "Fine fog" is the best description of such a picture as I have observed in portions of adrenals from cholesterolized rabbits and it is not unlike the appearance of tubules of the kidneys infiltrated with cholesterol. In sections of the liver, in which the anisotropic infiltration appeared in compact radial sparkling columns, these often stopped abruptly, but it could be seen that sometimes beyond such heavily infiltrated liver cells there were in the same columns stray masses of presumably the identical substance, but so scanty in amount that they appeared only as dull silvery shreds. With the high power lens the orange red substance in the infiltrated tubules appeared as extremely fine granules, such tubules looked as if powdered. This was an average appearance. However, in a few cases, particularly in Rabbit 11, there were larger granules in addition to this dustlike substance and we might conclude that these were the typical cholesterol esters. They were not neutral fat, even if large they never had the even contour or the red color of the fat droplets. Yet they did not flash up as anisotropic droplets under the micropolariscope. We must therefore conclude that these were cholesterol compounds which are not anisotropic. I have convinced myself that the cholesterol esters, which appear as doubly refractive substances, are not all identical in their characteristics. At least there are variations when the tissues have been fixed in formalin. The melting point is not the same, in fact there is quite a range of temperature within which these substances may melt, on cooling they do not all reappear as droplets with the cross figure, an observation

quantity of urine was sufficient the cholesterol content was determined by the colorimetric method. The figures given in the table are probably a little lower than they should be, because some of the sediment was used for microscopic examination. Epithelial cells were found in only a few cases and always in small numbers, casts were observed in only one instance. In several rabbits the urine was very thick and creamy.

Hypercholesterolemia occurs regularly in chronic nephritis, according to Weltmann,<sup>9</sup> Bacmeister and Henes,<sup>10</sup> Chauffard, Laroche and Grigaut,<sup>14</sup> Widal, Weill and Laudat.<sup>15</sup> Weltmann could not demonstrate an obviously constant dependence of the serum cholesterol on the gravity of the renal disturbances, while Bacmeister and Henes believe that it runs parallel with the degree of the generally impaired condition of health. Amyloid kidney is also associated with an increase of the blood cholesterol. Doubly refractive substances have been found in the sediment of the urine in chronic nephritis and in amyloid kidney by Lavrinovich<sup>16</sup> and Secchi.<sup>17</sup> There is no constant relation between the cholesterol content of the urine and blood according to Ferré, Mauriac and Defaye.<sup>18</sup> Quantitative analyses of the kidneys for their content in fat and fatlike substances have not had uniform results (Thaissen and Hess,<sup>19</sup> Rosenfeld,<sup>40</sup> Orgler<sup>41</sup>), Lohlein<sup>42</sup> bases his strict distinction between "fat infiltration" and "fatty degeneration" on the pathologic and clinical differences. In the former droplets consisting

33 Bacmeister and Henes. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Krankheiten. Deutsch. med. Wchnschr., 1913, *xxxix*, 544.

34 Grigaut. Dosage comparé de la cholestérine dans le sérum et dans les œdèmes, *Compt. rend. Soc. de biol.*, 1911, *lxv*, 317.

35 Weill and Laudat. Étude comparative du taux de la cholestérine libre et de ses éthers dans le sérum sanguin, *Soc. de biol., Compt. rend. hebdomadaire de séance*, 1913, *lxxiv*, 882.

36 Lavrinovich. Cholesterin Esters in the Urine, *Jour. Am. Med. Assn.*, 1914, *lxiii*, 1615, abstract from the original article in *Russk. Vrach.*, 1914, *xiii*, 19.

37 Secchi. Sul valore clinico dei lipoidi birfrangenti nell'urina, *Bull. Sc. Med.*, 1914, p. 83.

38 Ferre, Mauriac and Defaye. Sur la quantité de cholestérine contenue dans certains liquides normaux ou pathologiques de l'organisme, *Compt. rend. Soc. de biol.*, 1912, *lxxiii*, 141.

39 Thaissen and Hess. Beiträge zur physiologischen Chemie des Cholesterins und der Cholesterinester, *Biochem. Ztschr.*, 1914, *lxii*, 89 and 115.

40 Rosenfeld. Ueber Organverfettung, *Verh. d. 20. Kongr. f. inn. Med.*, 1902, 235.

41 Orgler. Ueber Beziehungen zwischen chemischem und morphologischem Verhalten pathologisch veränderter Nieren, *Verhandl. d. deutsch. path. Gesellsch.*, 1903, *vi*, 76. Chemische Niereuntersuchungen unter Berücksichtigung des histologischen Bildes, *Virch. Arch. f. path. Anat.*, 1904, *clxxvi*, 413.

42 Ueber die in pathologisch veränderten Nieren sichtbar werdende fettähnliche Substanz, *Verhandl. d. deutsch. path. Gesellsch.*, 1904, *viii*, 33. Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, *Virch. Arch. f. path. Anat.*, 1905, *cxviii*, 1.

exclusively of "fat" are accumulated in the epithelial cells of the tubules, involving either the entire parenchyma or such portions as are morphologically connected. The infiltrated cells are not injured, and albuminuria is not an associated feature in this condition. "Fatty degeneration," on the other hand, is characterized by focal deposits of highly refractive substances in the parenchyma, especially in the cortex. The epithelial cells are gravely damaged, and fat and fatlike substances occupy the intertubular tissue. Clinically, albuminuria is generally observed. This fatlike substance found in the kidney in pathologic conditions was at first considered as "protagon" (Stoerk,<sup>43</sup> Orgler,<sup>44</sup> Lohlein<sup>42</sup>), however, Panzer<sup>45</sup> reported that procedures applicable to the demonstration of protagon proved to be of no avail with kidneys morphologically rich in doubly refractive substances, while with proper measures for the extraction of this lipid, cholesterol and cholesterolesters were obtained. Several large white kidneys were thus analyzed.

The cholesterol infiltration of the kidneys of rabbits apparently resembles certain pathologic conditions in the human kidney, such as the large white kidney. This fact is of value, as we have to take into account that an infiltration of the liver such as occurs in rabbits is scarcely analogous to processes of the liver in man. How can we conceive of a spontaneously produced cholesterol infiltration in the human kidney? It is likely that the maintenance of the cholesterol equilibrium is dependent on the interaction of the various components of a regulating apparatus, the composition and the exact working of which we do not yet know. Derived from the food, as seems to be established, cholesterol forms a constituent of the cells of all the tissues and is present in all the normal and pathologic fluids of the body. It is stored in some organs and tissues, which seem to be cholesterol depots, such as the adrenal, the ovary and the adipose tissue. The close relationship, embryologically, between the kidney, the adrenal and the ovary may account for the relatively high normal cholesterol content of the kidney and the ready infiltration with this substance in pathologic conditions. The normal cholesterol content of the blood remains the same within certain limits. It rises and falls according to physiologic and pathologic conditions, which, apart from any transitory hypercholesterolemia following a diet rich in cholesterol, is probably entirely independent of food as hypercholesterolemia occurs.

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43 Ueber Protagon und uber die grosse weisse Niere, Sitzungsber. d. k. Akad. d. Wissensch., Math.-naturw. Klasse, Wien, 1905, cxv, 31.

45 Panzer. Ueber das sogenannte Protagon der Niere, Ztschr. f. physiol. Chem., 1905, xlviii, 519. Doppeltbrechende Substanzen aus pathologischen Organen, Ibid., 1907, lvi, 239.



in inanition (Rothschild,<sup>16</sup> Terrone,<sup>46</sup> Mayer and Schaeffer,<sup>47</sup> Ellis and Gardner<sup>48</sup>) The causes of such increase of the blood cholesterol are presumably manifold, but the processes may be chiefly that cholesterol is mobilized from depots and is also liberated from cells of functioning organs by metabolic and catabolic processes in physiologic conditions Physical as well as chemical factors may be at work In a measure, as these oscillations in the cholesterol content of the blood occur and reoccur and pathologic conditions exist to retard and hinder the exact working of the entire machinery, cholesterol may be taken up more readily than under normal conditions, by cells which have been bathed in and irritated by hypercholesterolemic blood The causes which lead to the development of a large white kidney and to the development of the nephritis of pregnancy, may be those which produce a frequent hypercholesterolemia, cause and effect may here be in reciprocal interaction In morbid conditions from many causes, there is probably a more or less prolonged instability of the cholesterol equilibrium, and insufficiency of one component ordinarily concerned chiefly in the regulation of the equilibrium, as the liver is supposed to be, throws greater demands on other organs which are physiologically less prepared for such work, if in addition the cells are debilitated, they will soon be incapacitated and cholesterol will not be disposed of to an extent proportionate to the requirements, but will be deposited in excess and will act with destruction like a foreign body

#### SUMMARY

In experimental hypercholesterolemia the effects vary, not only according to the kind, size, and number of the doses, but also greatly according to the general condition of the rabbit, individual as well as physiological and pathological The amount of cholesterol seems less essential than the degree of constitutional integrity and functional activity of the cell which prevails prior to the injection, or which results from the first establishment of an experimental hypercholesterolemia

The ready infiltration in the liver of the rabbit, in contrast to that of carnivora, is an expression of insufficiency on the part of an organ which has normally a light task to perform in the cholesterol metabolism

46 Terrone Nouvelles recherches sur l'influence de l'inanition et de la suralimentation sur la teneur des tissus en substances grasses et en cholestérine, *Jour de physiol et de path gen*, 1914, xvi, 408

47 Mayer and Schaeffer Variations de la teneur des tissus en lipoides et en eau au cours de l'inanition absolue *Activite physiologique des tissus*, *Jour de physiol et de path gen*, 1914, xvi, 203 and 244

48 Gardner The origin and testing of cholesterol in the animal organism, IX On the cholesterol content of the tissues, other than liver, of rabbits under various diets and during inanition, *Proc Roy Med and Chir Soc*, 1912, lxxxv, 385

As a result of hypercholesterolemia gallstones may be formed in sterile bile without infection or injury of the gallbladder. Their formation is preceded by desquamation of the epithelial cells, due to the irritating action of an excess of cholesterol.

Cholesterol injected into the circulation of rabbits is not accumulated in the blood to any large degree, but is rapidly deposited in various organs, while the elimination of it through the bile and urine is also greatly increased.

The focal infiltration of the kidney with cholesterol which occurs in hypercholesterolemia is accompanied by degenerative processes of the parenchymatous structures. The urine, as a rule, contains appreciable amounts of cholesterol.

# A PHARMACOLOGIC AND CLINICAL STUDY OF PAPAVERIN<sup>1</sup>

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Papaverin is one of the principal primary opium alkaloids in point of both quantity and pharmacologic interest. Its amount in opium varies from 0.1<sup>1</sup> to 0.2<sup>2</sup> per cent. The alkaloid was discovered by Merck in 1848. It crystallizes in white prisms, with a melting point of 147° C. The crystals are insoluble in water and alkalis, difficultly soluble in ether and benzol, but easily soluble in warm alcohol, chloroform and acetone. It is tasteless, is neutral in reaction with litmus and is polariscopically inactive. The alkaloid easily combines with acids, forming salts, and it is the sulphate and more especially the hydrochlorid that are chiefly used in physiologic work. These salts can be obtained on the market in a very pure chemical state, and are soluble in water and in normal saline. Like all the other opium alkaloids, papaverin is characterized by color reactions by which it can be identified and distinguished from the others. These color reactions have been recently well described by Warren<sup>3</sup>. The most characteristic are the deep rose color produced by Marquis' reagent (sulphuric acid plus formaldehyd) and the greenish-blue color produced by potassium ferricyanid and Marquis' reagent<sup>4</sup>.

The empirical formula for papaverin is  $C_{20}H_{21}NO_4$ . Its chemical structure has been thoroughly worked out and is of great interest, not only in itself, but also as throwing light on the constitution of other opium alkaloids. A thorough analysis of its constitution finally enabled Pictet and Gams<sup>5</sup> to prepare it synthetically. Papaverin belongs to the so-called benzyl-isoquinolin group of opium alkaloids,<sup>6</sup>

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\* From the Departments of Pharmacology and Medicine, Johns Hopkins University

1 Simon. Dissertation, Bern, 1903

2 Henry. The Plant Alkaloids, 1913

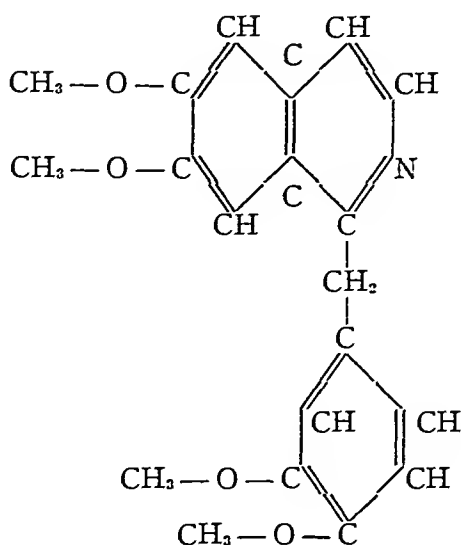
3 Warren. Am Jour Pharm, 1915, LXXVII, 439

4 Warren. Jour Am Chem Soc, 1915, XXXVII, 2402

5 Pictet and Gams. Beitr z Klin d Tuberk, XLII, 2943

6 Winterstein and Trier. Die Alkaloide, 1910, p. 160

the principal other constituent of which is narcotin Its complete structural formula is as follows



### I PHARMACOLOGY

The earlier pharmacologic experiences with papaverin are very few and limited We need consider only the works of Claude Bernard and Baxt Claude Bernard<sup>7</sup> denied to papaverin any narcotic properties, and classed it as a convulsant closely related to thebain This view, which is a rather exceptional one, is as remarkable as the same author's attribution of powerful narcotic properties to the comparatively inert narcein Sichting<sup>8</sup> from observations on himself and other human subjects concluded that papaverin is a mild narcotic The most important and comprehensive of the earlier works on papaverin is that by Baxt<sup>9</sup> Basing his conclusions on many animal experiments, Baxt claimed that papaverin is possessed of marked narcotic properties and is but slightly toxic for higher animals The same author also called attention to its effect upon the frog's heart Von Schroeder,<sup>10</sup> in his classic paper on the opium alkaloids, takes stand midway between Claude Barnard and Baxt, attributing to papaverin mild narcotic properties and also calling attention to the slowing of the frog's heart after injection of the drug It is surprising to note that he failed to observe a fall in blood pressure, which is one of its striking characteristics

Of the recent works on papaverin, by far the most important has been done by Pal of Vienna<sup>11</sup> and his school To Pal belongs the

7 Cl Bernard Compt rend Acad d sc lxx, 464

8 Sichting Dissertation, Bonn, 1869

9 Baxt Arch f Anat u Physiol, 1869, p 112

10 Von Schroeder Arch f Exper Path u Pharmacol, 1883, xvii, 96

11 Pal Deutsch med Wchnschr, 1913, pp 395, 2068, 2514, Wien med Wchnschr, 1913, p 1049, Zentralbl f Physiol, 1902, p 68

credit especially of calling attention to the action of papaverin on smooth muscle. It is strange to note, however, that although Pal has written much on the subject and tried the drug extensively in the clinic he has published, with the exception of his work on the intestinal muscle, very few experimental data on the subject.

A more careful pharmacologic study of papaverin by the most modern methods was desirable, and it was undertaken by the present author in connection with a general study of the opium alkaloids individually and in combination with each other. The results were so interesting and so fraught with therapeutic possibilities, that it is deemed well to describe the pharmacology of papaverin with a few clinical experiences in a separate paper.

The most important pharmacologic properties of papaverin may be considered under four headings—its effect on the circulation, its effect on the respiration, its analgesic effect, and its action on smooth muscle structures.

#### A ACTION ON CIRCULATION

*Effect on the Heart*—If we excise a frog's heart and perfuse it with a weak solution of papaverin hydrochlorid (0.001 per cent or less) in physiologic saline solution, a distinct slowing of the heart beat is noted, together with an increase in the toxicity of the heart muscle and more powerful contractions. If a stronger solution of papaverin is used (0.01 to 0.1 per cent), the stimulating action is absent, and instead, a greater slowing of the beat and relaxation of the heart muscle are produced. Still stronger solutions lead to a further slowing and relaxation, and very often a heart-block effect is noted, the auricle beating oftener than the ventricle in the ratio of 2 to 1, 3 to 1 or even 4 to 1. Finally the heart comes to a standstill in diastole. This peculiar heart-block action is very similar to that produced by the closely allied alkaloid narcotin, as described by the author elsewhere<sup>12</sup>. Both Baxt and von Schroeder noted the toxic effect of large doses of papaverin on the frog's heart, but they failed to note the stimulating action of the drug when given in small doses (Fig. 1).

The stimulating action of papaverin on the heart is much better shown in mammalia and was studied by the author in the rabbit, cat and dog. This was done in part by perfusing excised hearts according to the methods of Martin or Langendorff, but was much more satisfactorily demonstrated by the study of the heart in situ with the chest opened, and the circulation intact. By the use of a cardiac plethysmograph or by direct myocardiographic tracings, it was found that small doses of papaverin produced a slight slowing of the heart beat and a marked increase in the tonicity of the heart muscles. The strength of the contractions and the volume output were also increased.

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12 Macht. Am Jour Med Sc, in press

That this effect was not due to the action on the cardio-inhibitory center, was shown by cutting the vagi. That it was not due to the action of papaverin on the cranial autonomic nerve terminals in the heart, was shown by administering atropin, which paralyzed the vagus endings, but did not change the effect of papaverin. That this action on the heart was not due to any effect on the cardio-accelerator

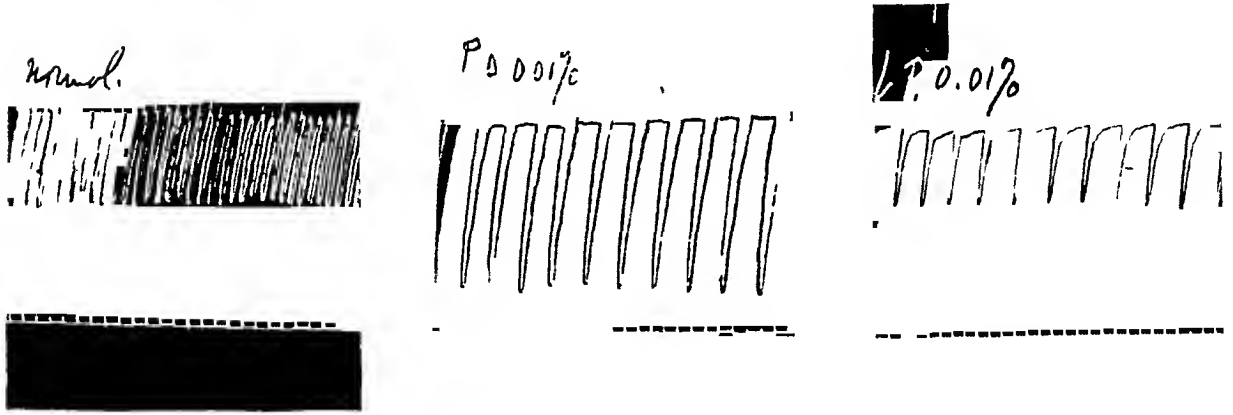


Fig 1—Effect of papaverin on a frog's heart. The down stroke represents the systole. Note slowing and increased contraction by a small dose (0.001 per cent), and toxic effect of larger dose (0.01 per cent).

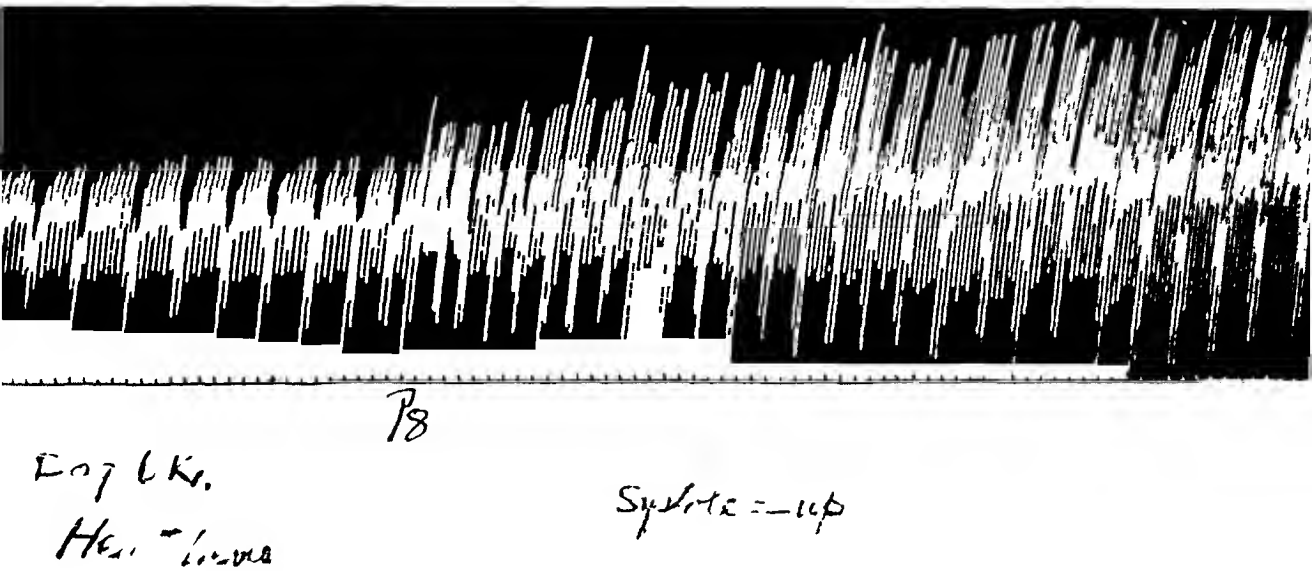


Fig 2—Action of papaverin on heart of dog, myocardial tracing

mechanism, was shown by destroying the stellate ganglia. The stimulant effect was found to be due to a distinct action on the heart muscle itself or the ganglia in it. This was proved by experiments on decerebrated animals, on special preparations according to Sherrington,<sup>13</sup> and on excised frogs' and terrapins' hearts (Figs 2 and 3).

<sup>13</sup> Sherrington Jour Physiol, 1909, XXXVIII, 375

Large doses of papaverin had relatively the same effect on the mammalian heart as on the frog's heart. They produced excessive slowing and paralysis of the heart, at which stage the toxic effect on the central nervous system also generally manifested itself in the form of convulsions.

Closely associated with the action on the heart is the effect of papaverin on the coronary arteries and the coronary circulation. This effect has been treated fully in a study of the effect of the principal opium alkaloids on the coronary circulation, published elsewhere,<sup>17</sup> and we will therefore merely sum up our findings here.

The action on the coronary circulation was studied in three ways: first by perfusion of excised hearts, especially by the recent method of Kiafko<sup>15</sup>; second, by the study of excised rings of the coronary artery, and third, by ascertaining the effect on the coronary circulation

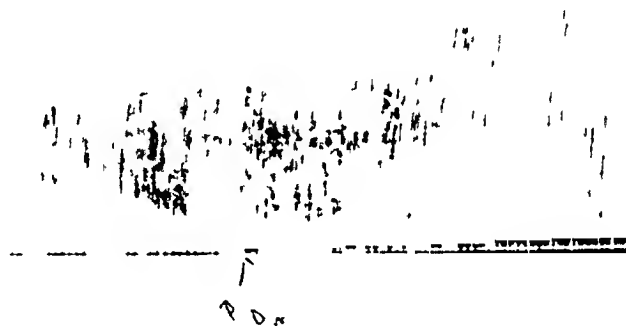


Fig 3—Action of papaverin on cat's heart. Heart is in a plethysmograph, the systole being represented by the down stroke.

in the living animal with chest opened and heart in situ, by recording the blood drop-flow from a wounded coronary artery, the blood having previously been hirudinized to prevent coagulation.<sup>16</sup>

By all the three methods it was found that papaverin is a powerful dilator of the coronary artery. Figure 4 shows this dilator effect on an arterial ring.

The following protocol illustrates the coronary dilatation as shown by Krakoff's method.

*Experiment 10*—Perfusion of pig's heart by Krakoff's method. The normal drop-flow was 25 drops per minute, after perfusion with 0.02 per cent papaverin hydrochlorid solution the drop-flow was 46 drops per minute, five minutes later it became 56 drops per minute.

14 Macht. Jour Am Med Assn, 1915, xlv, 1489.

15 Krafkoff. Arch f d ges Physiol (Pfluger's), 1914, clvii, 501.

16 Bond. Jour Exper Med, 1910, xii, 575.

Figure 5 illustrates the increase in coronary circulation as indicated by the increased number of the blood drops flowing from an incised coronary in a hirudinized cat

The coronary ring method could be practiced on the human as well as other coronary arteries, and it gave the same results

*Effect on the Blood Pressure*—The effect of a drug on blood pressure is a resultant of its effect on the heart, on the vasomotor appa-

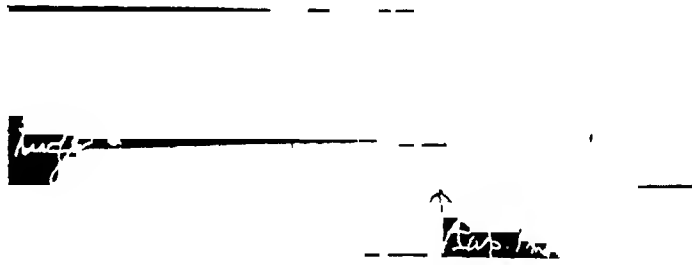


Fig 4—Action of papaverin on pig's coronary artery, three rings in chain; stretching weight 38 gm, lifting weight 18 gm Note relaxation

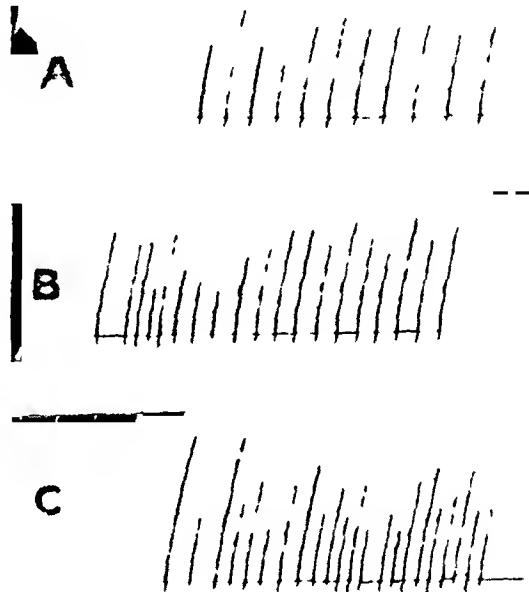
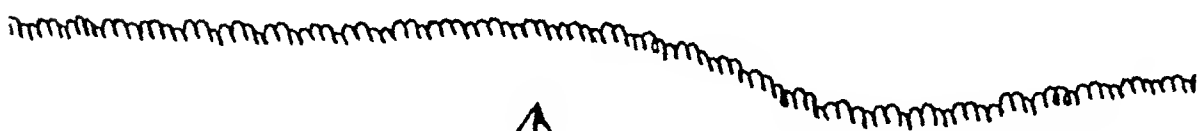


Fig 5—Experiment performed Dec 22, 1914, on a cat of 25 kg, under ether anesthesia, and hirudin 20 cc Study of blood-flow from wounded coronary artery by Bond's method *A*, normal drop-flow, 11 per minute, *B*, drop-flow after injection of 8 mg papaverin hydrochlorid, 18 per minute, *C*, three minutes later, 26 per minute

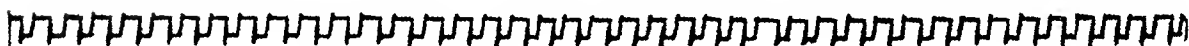
tus and on the vessels themselves These factors should be borne in mind in studying the effect of papaverin on the blood pressure The most striking effect of papaverin in any blood pressure experiment on a rabbit, cat or dog—and the same is also true in man—is a fall in pressure This fall in pressure was given after decerebrating the



respiration



Pap. hel.  
4 mgs.



Time in secs.

Fig 6—Experiment performed January, 1915, on a cat of 25 kg, ether anesthesia, showing effect of papaverin on blood pressure

Pap. hel 5 mgs  
↓

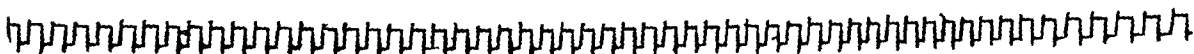


Fig 7—Experiment performed January 1915 ether anesthesia, showing effect of papaverin on blood pressure with vagi cut

animal through the orbit and also in Sherrington's spinal preparations. It follows, therefore, that the alkaloid produces the fall in pressure chiefly through its peripheral effect on the vessel walls themselves. The following curves and protocols will illustrate the above points.

Protocol 1 Experiment was performed Oct 29, 1914, on a cat of 4 kg. Under ether anesthesia a spinal cord preparation, according to Sherrington, was made and curara administered. Normal blood pressure, 84 mm, normal pulse, 68 per 30 seconds. Papaverin hydrochlorid, 15 mg, was injected into femoral vein. One minute after, blood pressure was 64 mm, pulse, 68 per 30 seconds, five minutes after blood pressure was 70 mm, pulse, 70 per 30 seconds.

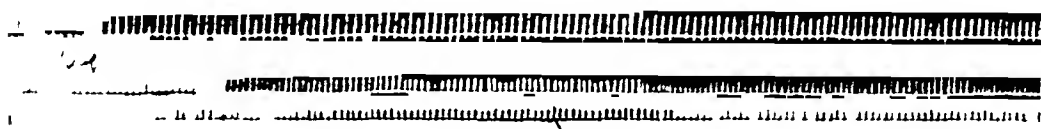


Fig 8—Perfusion of hind legs of *Rana pipiens*. Upper line gives number of drops on perfusing with normal saline, second line gives number of drops on perfusing with papaverin hydrochlorid, 0.01 per cent solution in normal saline, lower line indicates time in seconds.

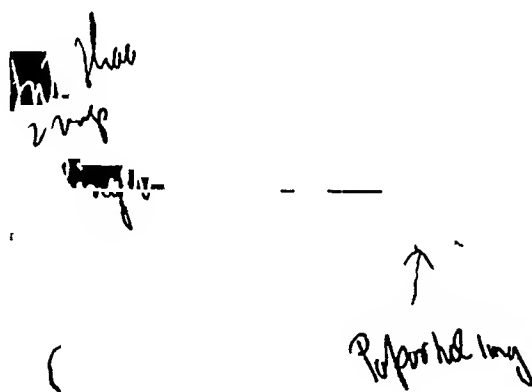


Fig 9—Action of papaverin on internal iliac artery of pig. Two rings, stretching weight 30 gm, lifting weight 16 gm.

Protocol 2 Experiment was performed Jan 8, 1915, on a cat of 2.5 kg. Under ether anesthesia decerebration was performed through the orbit. The normal blood pressure was 72 mm, pulse, 65 per 30 seconds. Papaverin hydrochlorid, 10 mg, was injected into femoral vein. One minute after, blood pressure was 56 mm, pulse, 66 per 30 seconds, five minutes after blood pressure was 66 mm, pulse, 65 per 30 seconds.

*Action on Blood Vessels*—The vasodilating action as noted in the blood pressure experiments could be shown by other methods.

The effect on the frogs' blood vessels was shown by perfusion of the hind legs by Trendelenburg's method. The action on the mammalian vessels was studied by means of arterial rings or strips.

described by the author elsewhere<sup>17</sup> By this method it was interesting to note that different vessels differed in their reaction to papaverin Whereas the coronary arteries, the carotids and subclavians, and internal and external iliacs were markedly relaxed by the drug, the pulmonary artery was but slightly dilated and the uterine arteries still less so The effect on the mesenteric and splanchnic vessels was studied by means of the plethysmograph, and as might have been expected from the marked fall noted in blood pressure experiments, they were greatly dilated This is well illustrated by the figures

Summing up the circulatory effect of papaverin, we may therefore say that it causes a fall in blood pressure, which is due partly to its effect on the brain, but chiefly to its peripheral action, that it produces a marked vasodilatation, especially of the peripheral and splanchnic vessels, that it increases the coronary circulation, and that, in small

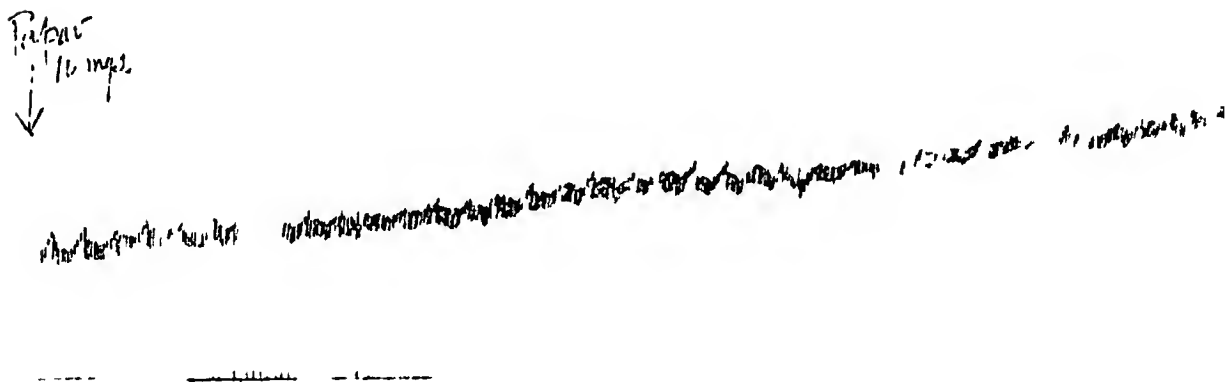


Fig 10—Effect of papaverin on intestinal vessels, as recorded by a plethysmograph Curve upward indicates vasodilatation

doses, it slows the heart, at the same time tending to increase the strength of its contractions

#### B ACTION ON THE RESPIRATION

The action of papaverin on the respiration has been touched upon by the author in another paper dealing with the action of opium alkaloids in general on the respiration<sup>18</sup> There it was pointed out that the pharmacologic study of the respiration is a complex matter It is not sufficient merely to determine the rate and volume output of respiration Drugs may affect the respiratory function in several ways by acting upon the respiratory center directly, by producing changes in metabolism, by altering the mechanical conditions of the

17 Macht Jour Pharmacol and Exper Therap, 1914, vi, 13

18 Macht Jour Pharmacol and Exper Therap, 1915, vii, 339

chest and abdomen, by acting on the bronchoconstrictors or bronchodilators, and indirectly by changes in the cerebral circulation, etc. Accordingly, in studying the action of papaverin on the respiration, observations were made on the rate of respiration, the total volume of air respired per minute or *total ventilation*, the true or *alveolar ventilation*, the effect on the respiratory center, and the effect on the bronchi. By the method described in the paper referred to, it was found that papaverin, while producing a slight narcotic effect upon the animal, exerts a distinctly stimulating effect on the respiration. While the rate of respiration is slightly decreased, the volume output and

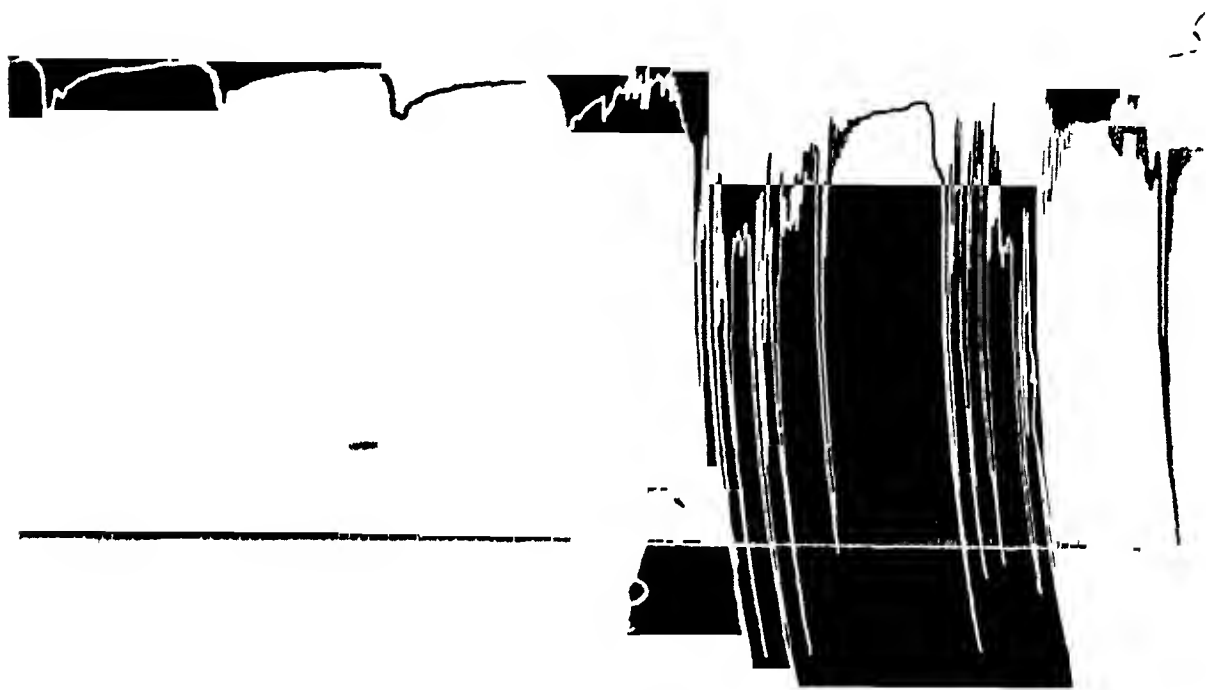


Fig 11—Experiment performed April 27, 1915. Perfusion of respiratory center by Hooker's method in a dog weighing 7.5 kg. At *P* 2 mg of papaverin hydrochlorid were introduced. Note stimulation of center.

alveolar ventilation are markedly increased. The respiratory center is quite active as shown by its lively response to carbon dioxide inhalations, and the dead space is greatly enlarged, indicating a bronchodilatation. The bronchodilator effect was also proved directly by experiments with bronchial rings. The stimulating action of papaverin on the center was furthermore corroborated directly by perfusion of the medulla by Hooker's method.

The following protocols illustrate the above findings, and Figure 11 shows the result of a papaverin experiment on the medulla.

Experiment was performed Feb 24, 1915, on a rabbit of 1,150 gm, 11 a m, rabbit tied down and allowed to get quiet

Time	Breathing	Rate per min	Vol per min, c c	Vol per resp, c c
11 30 a m	Air of room	68	450	66
	CO <sub>2</sub> 5%	68	540	79
	CO <sub>2</sub> 10%	68	640	94

11 50 a m, injected subcutaneously papaverin hydrochlorid, 8 mg

Time	Breathing	Rate per min	Vol per min, c c	Vol per resp, c c
12 15 p m	Air of room	60	480	80
	CO <sub>2</sub> 5%	64	520	81
	CO <sub>2</sub> 10%	66	660	100
1 30 p m	Air of room	54	470	87
	CO <sub>2</sub> 5%	60	520	87
	CO <sub>2</sub> 10%	60	800	133
2 30 p m	CO <sub>2</sub> 5%	58	500	86
	CO <sub>2</sub> 10%	60	800	133

Experiment was performed March 11, 1915, on a rabbit of 910 gm  
2 00 p m, animal tied down and allowed to quiet itself

Time	Breathing	Rate per min	Vol per min, c c	Vol per resp, c c
3 00 p m	Air of room	48	100	20
	CO <sub>2</sub> 5%	46	200	43

Alveolar CO <sub>2</sub>	57 per cent
CO <sub>2</sub> of expired air	17 per cent
Alveolar ventilation	298 per cent
Calculated dead space	15 c c

3 35 p m, injected subcutaneously papaverin hydrochlorid, 3 mg

Time	Breathing	Rate per min	Vol per min, c c	Vol per resp, c c
4 05 p m	Air of room	40	230	57
	CO <sub>2</sub> 5%	40	400	100

Alveolar CO <sub>2</sub>	68 per cent
CO <sub>2</sub> of expired air	18 per cent
Alveolar ventilation	608 c c
Calculated dead space	42 c c

#### C ACTION ON SMOOTH MUSCLE STRUCTURES

Attention to this remarkable property of papaverin has been called by Pal, to whom we are indebted for arousing interest in the subject. Pal made a broad generalization to the effect that the alkaloid lowered the tonus and produced relaxation of all smooth muscle structures, without paralyzing them.

This generalization seems to have been based chiefly on Pal's clinical experiences, as his published experimental work is confined chiefly to studies of intestinal muscle. It is remarkable, however, to find that later observations by other investigators and the experimental work of the present author all seem to confirm fully the truth of Pal's

statement The present author studied the action of papaverin on all kinds of smooth muscle organs, some of which had already been investigated and others of which were never examined, and found that in all cases the alkaloid produced a relaxation of smooth muscle

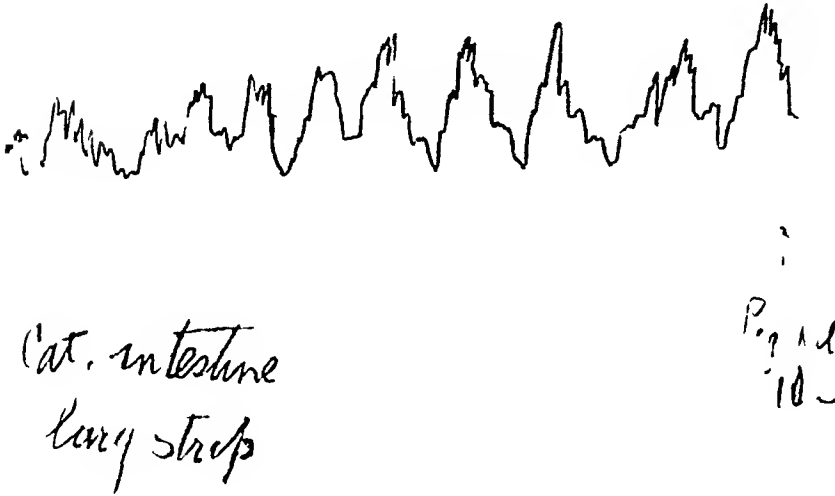


Fig 12—Action of papaverin on longitudinal muscle of cat's intestine

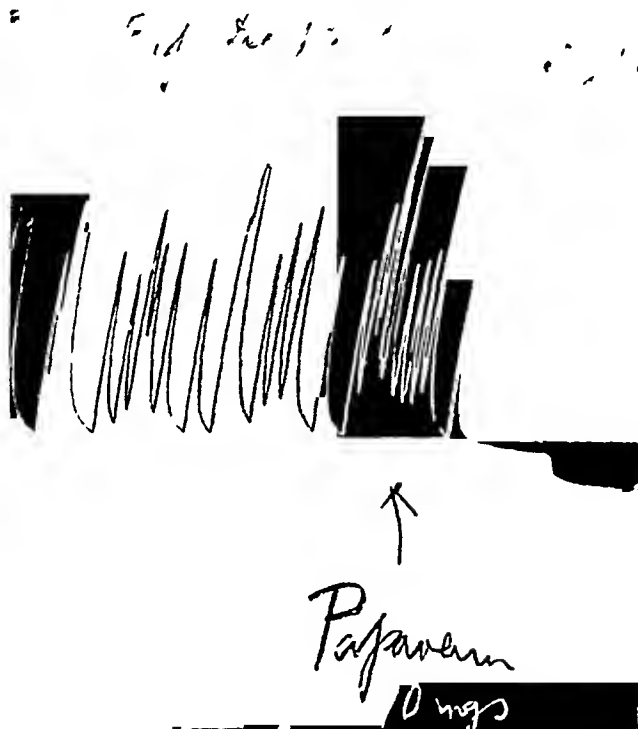


Fig 13—Action of papaverin on ureter of pig, three hours after excision  
Upward stroke indicates the contraction

The effect on blood vessels and bronchi has already been mentioned The subjoined illustration (Fig 12) shows the effect on intestinal muscle strips The same result was found with strips of the

uterus and the bladder. In experiments on excised pyloric sphincters the present author could confirm the clinical experiences of Pal in pylorospasm. A relaxation of the sphincter was noted. Furthermore, one of the most interesting effects of papaverin to be mentioned in this place is its effect on the ureter. The present author found that this drug produces a marked relaxation of that organ and this effect is of practical interest as will be shown later (Fig. 13).

#### D ANALGESIC PROPERTIES

Attention to the narcotic and analgesic properties of papaverin has been especially directed by Baxt. That author claimed for the drug these properties in a high degree. Frommüller<sup>19</sup> also emphasized the analgesic effect of papaverin. On the other hand Claude Bernard, Sichtung, Eulenburg<sup>20</sup> and von Schroeder, considered the alkaloid in this respect as of very little importance. The explanation for the wide differences of opinion on the subject was chiefly due to the lack of an adequate method of comparing the effect of opium alkaloids on pain quantitatively. In a paper on the subject published elsewhere, the present author elaborated a simple method for a quantitative study of pain stimuli on the surface of the body and the effect of papaverin was investigated in that connection.<sup>21</sup>

It was found that papaverin possesses analgesic properties in a higher degree than codein, the effect of 40 mg. being not much inferior to that produced by 10 mg. of morphin. The onset of the analgesia, however, was much slower and its duration shorter. The general narcotic effect and depression of the higher centers was, on the other hand, much less than that from morphin.

Observations were made on six normal individuals, and the results, barring slight individual variations, agreed in all cases. The following protocols will serve as illustrations. It will be noted that injections of papaverin are slightly painful at the site of injection, but this discomfort soon passes away.

#### E TOXICITY

Before discussing the therapeutic applicability of papaverin, it is essential to consider its toxicity. Papaverin is not a very poisonous drug and comparatively large doses of it can be given without dangerous results. Indeed the lethal dose for higher animals is so large that for economic reasons it was not deemed profitable to push the drug till death was produced in too many experiments. It was suffi-

19 Frommüller. Klinische Studien über narkotische Arzneimittel, Erlangen, 1869.

20 Eulenburg. Die Hypodermotische Injection der Arzneimittel, Berlin, 1867.

21 Macht, Herman, and Levy. Jour. Pharmacol. and Exper. Therap., 1916, viii, 1.

TABLE 1—EXPERIMENT PERFORMED JULY 10, 1915, 2 20 P M	
Subject D I M Injection of papaverin sulphate, 40 mg	
H ind	

	Hand			Tongue			Lip			Nose		
	Position of Secondary, Cm	Kro necker Units	C G S Units	Position of Secondary, Cm	Kro necker Units	C G S Units	Position of Secondary, Cm	Kro necker Units	C G S Units	Position of Secondary, Cm	Kro necker Units	C G S Units
Normal	11.8	155	2,820	14.4	55	1,173	16.8	26	639	17.7	20	518
30 min after injection	10.2	270	5,313	12.9	100	1,897	14.0	63	1,346	14.6	51	1,139
1 hr after injection	9.7	320	6,210	12.4	125	2,277	13.3	87	1,656	12.2	137	2,484

Remarks—Pulse before injection, 72, after injection, 66, blood pressure before, systolic, 107, diastolic, 80, after, systolic, 98, diastolic, 78  
head after injection, slight pain at place of injection, very slight feeling of heaviness and fullness in ears, no constipation

Subject D I M Injection of papaverin sulphate, 40 mg

Subject C S L Injection of

TABLE 2—EXPERIMENT PERFORMED JULY 8 1917

Hand	Subject C S L	EXPERIMENT PERFORMED JULY 8, 1915, 2 20 P M	Injection of papaverin hydrochlorid, 40 gm

EXPERIMENT PERFORMED JULY 8, 1915, 2 20 P M							
Subject C S L Injection of papaverin hydrochlorid, 40 gm							
	Hand		Tongue		Lip	Nose	
	Position of Secondary, Cm	Kro necker Units	C G S Units	Position of Secondary, Cm	Kro necker Units	O G S Units	Position of Secondary, Cm
Normal	10 0						
15 min after injection							



TABLE 3—EXPERIMENT PERFORMED JULY 15, 1915, 10 40 A M  
Subject N B H Injection of papaverin hydrochlorid, 35 mg

	H ind			Tongue			Lap			Nose		
	Position of Secon dary, Cm	Kro necker Units	C G S Units	Position of Secon dary, Cm	Kro necker Units	C G S Units	Position of Secon dary, Cm	Kro necker Units	C G S Units	Position of Secon dary, Cm	Kro necker Units	C G S Units
Normal	13.2	89	1,725	19.0	15	408	16.0	31	778	19.7	13	311
20 min after injection	12.5	120	2,208	18.2	17	464	14.8	18	1,070	18.3	17	449
40 min after injection	12.3	130	2,346	18.1	17	474	14.6	51	1,139	18.0	18	483

Remarks—Pulse before injection, 70, after injection, 64 Systolic pressure before injection 108, after injection 103 No discomfort following injection, except slight soreness of arm, no constipation, no nausea

cient for all practical purposes to ascertain the quantity of the drug which produced toxic symptoms

In the frog it was found that the minimal lethal dose was about 1 mg per gram weight of frog. These results agreed well with those of von Schroeder

In the guinea-pig 100 mg administered subcutaneously stimulated respiration, 200 mg produced violent convulsions, and death in about ten minutes. A similar experience with guinea-pigs is reported by Bradbury<sup>22</sup>

White mice required about 0.5 mg per gram weight to produce convulsions and death in half an hour

In rats, according to Bradbury, 300 mg produced weakness of the muscles, but no death

In the case of rabbits different experimenters show considerable variations in their figures. According to Bradbury it required 480 mg to produce death. Kunkel<sup>23</sup> claims that doses up to 1 gm produce muscular weakness, and larger doses produce convulsions and death, but he does not state whether the drug was given by stomach or by injection. Lewin<sup>24</sup> gives 2 gm as the lethal dose by mouth. In the present author's experiments the drug was not pushed to a lethal outcome, but it was found that doses of 25 mg per kilo, subcutaneously, excited the animal, but did not cause death, while repeated doses of 10 mg each, every five to ten minutes, intravenously, caused convulsions, after five or six doses

In cats the present author found that 55 mg per kilogram, subcutaneously, produced no untoward symptoms. Repeated intravenous injections of 10 mg doses in cats of 2.5 to 3 kg produced convulsions after six doses

In dogs Baxt noted marked anesthesia after 100 mg. In the present author's experience subcutaneous injections of 50 mg per kilogram produced distinct narcosis with uneventful recovery. Intravenous injections in doses of 10 mg every five minutes produced convulsions in a dog of 6 kg after about 100 mg were injected

In reference to the safe dosage for man, we have collected considerable data. Schroff and Hoffman<sup>25</sup> state that doses of 450 mg produce no effect. Fronmüller injected subcutaneously 240 mg without harmful results. Leidesdorff<sup>26</sup> injected insane patients with doses of over 400 mg without danger. Blyth<sup>27</sup> puts 1 gm as the dosage

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22 Bradbury. *Lancet*, London, July, 1899

23 Kunkel. *Toxikologie*, 1901, II, 820

24 Lewin. *Toxikologie*, Berlin, 1897, p. 260

25 Schroff and Hoffman. *Wien med Wchnschr*, 1868, pp. 935 and 952

26 Leidesdorff. *Ztschr d Wien Aerzte*, 1868, LIII, 115

27 Blyth. *Poisons*, London, 1906, p. 322

limit, and Pal quotes Bouchut also as giving quantities up to 1 gm subcutaneously. These doses, however, are certainly not to be considered safe at present, and Lewin cites a case with some weakness produced by 180 mg. Pal recommends 40 to 80 mg subcutaneously as perfectly safe doses, and states that higher doses also produce no harmful results. The author's experience with the drug on himself, colleagues and patients certainly agrees with Pal's, so that doses of from 40 mg to 80 mg subcutaneously, in adults, may certainly be administered without trepidation.

The present author injected papaverin intravenously on three occasions without any untoward symptoms. It was found that 40 mg well diluted with 200 cc of saline and injected slowly could be administered safely.

No cumulative action from papaverin has been noted by the author. Repeated intravenous injections of from 10 to 20 mg of the hydrochlorid daily over periods of from two to three weeks showed no such effect in rabbits or dogs. Papaverin is for the most part unchanged in the body, and is excreted chiefly through the urine, bile, and partly through the small intestine.\*

## II CLINICAL EXPERIENCES

The clinical application of papaverin should of course follow its physiological behavior. This has been done, in a measure, by Pal and his school. Thus its peculiar effect on the circulation, promoting the coronary circulation, lowering the pressure and stimulating the heart, will suggest its use in angina pectoris and in cases with hypertension. Pal actually employed it in aborting uremic crises.<sup>29</sup>

Its stimulating effect on the respiratory center would suggest its use in cases where depression of that center is undesirable.

Its analgesic action would suggest its use as a substitute for morphin, especially where codein is not effective.

Lastly, its peculiar action on smooth muscle would indicate its use in all cases with visceral spasm.

In the present communication, the author is reporting his rather limited experience with the drug not so much as a positive proof of the therapeutic value of papaverin, as in order to stimulate further observation. The following cases were selected more or less at random, and papaverin was administered in some cases to relieve pain and in others for the purpose of exhibiting its other properties. The results seem to be encouraging.

On examining the histories, one will note that in regard to its pain-relieving quality papaverin, though inferior to morphin, is cer-

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\* Dragendorff. *Ermittlung von Giften*, 1895, p. 225.

28 Bouchut. Cited by Pal in *Med. Klin.*, Nov. 2, 1913, No. 44.

29 Pal. *Med. Klin.*, Nov. 2, 1913, No. 44.

tainly equally as efficient as, and even more efficient than, codein. It will also be noted that it was more or less efficient in the cardiac cases (Cases 14, 15, 22, 27, 28, 30). In the respiratory conditions the effect was not so marked, but attention is called to Case 5, in which it was efficacious in relieving the troublesome cough of an advanced consumptive, who was habituated to heroin, and its really striking relief of the cough in the case of aneurysm, No 7, which was not relieved by any other drug.

The employment of papaverin in bronchial asthma was recommended by Pal. In Case 10, the effect of papaverin on bronchial asthma in a boy of 15 years was immediate. Case 11, however, another case diagnosed as "asthma," was not relieved, but neither was that patient relieved by epinephrin or atropin.

Cases 13 and 25 illustrate the effect of papaverin in relaxing the spasm of biliary ducts, and other successful examples of the antispasmodic properties of the drug are found in Cases 12, 17, 18, and 21.

The peculiar property of papaverin in relaxing the tonus and contractions of smooth muscle organs led Pal to recommend it in cases of pylorospasm. Its value in such cases was demonstrated by Holz-knecht and Sgalitzer<sup>30</sup> through their Roentgen-ray studies, and it has recently been further recommended by Delprat<sup>31</sup>. All these authors administered papaverin by hypodermic injection. Inasmuch as a very striking effect is produced by the drug on smooth muscle *in vitro*, and that by very small doses, as shown by Popper,<sup>32</sup> it occurred to the present author that papaverin might in such cases be advantageously given by mouth, and in fact two or three cases of pylorospasm treated in this way in the Harriet Lane Home for Invalid Children (Professor Howland) gave favorable results.

Another application of the tonus-relaxing quality of papaverin suggested by the present author was its introduction directly into the ureter through a cystoscope, in cases of ureteral calculus and colic. Observations along this line are being carried on at the James Buchanan Brady Urological Institute (Professor Young). It may be here stated that two cases of ureteral stone were successfully treated by Dr. T. I. Gerathy in this way.<sup>33</sup>

#### SYNOPSIS OF CLINICAL CASES

CASE 1—S. M., dispensary case, F 39372. Acute gastric indigestion. Forty mg hypodermically. Slight relief.

CASE 2—M. G., dispensary case, E 91401. Severe cramps in one leg. Tablets 40 mg each, three times a day by mouth. Distinct relief.

30 Holz-knecht and Sgalitzer. *Munch med Wchnschr*, 1913, No 3.

31 Delprat. *Nederl Tijdschr v Geneesk*, 1915, 11, 1311.

32 Popper. *Arch f d ges Physiol (Pfluger's)*, 1913, cliii.

33 Gerathy and Macht. *Bull Johns Hopkins Hosp*, 1916, xxvii, 119.

CASE 3—A C, dispensary case, F 33848 Very persistent cough, tuberculosis Tablets 40 mg each, three times a day Slight relief

CASE 4—J Y, dispensary case, F 36190 Chronic bronchitis and emphysema, persistent cough Tablets 40 mg each, three times a day No relief

CASE 5—P R, outside case, white woman, 23 years of age Advanced tuberculosis Codem has no effect Dionin and heroin have very little effect because of habitual use for cough Tablets of papaverin, 40 mg each, patient says relieved her a little more than heroin

CASE 6—H M, dispensary case, E 58406 Tuberculous laryngitis and phthisis Marked relief of cough and pain from tablets of papaverin hydrochlorid, 40 mg

CASE 7—J B, dispensary case, F 38599 Aortic aneurysm, troublesome cough Patient tried morphin, heroin, codem, narcophin Finds that papaverin tablets, 40 mg each, relieve better than any other drug Same experience repeatedly

CASE 8—W D, dispensary case, E 59866 White man, 36 years of age Lumbago Relieved by injecting 40 mg of papaverin sulphate Pulse before injection 72, after injection 68 per minute

CASE 9—S G, outside case White man, 35 years of age Acute gastric indigestion Injection of 40 mg papaverin sulphate with slight relief Pulse before injection 88, after injection 72 per minute

CASE 10—B H, outside case White boy, 15 years of age Bronchial asthma Injection of 30 mg papaverin sulphate Immediate relief

CASE 11—Dr L Karlinski's case White woman "Asthma" Papaverin injection does not relieve Epinephrin injection gives no relief, but aggravates condition Only drug giving any relief is morphin

CASE 12—R A, outside case White woman, 26 years of age Uterine colic Relieved by injection of 40 mg papaverin sulphate

CASE 13—R S, dispensary case, F 30928 White woman, 32 years of age Gallstone colic Two attacks, at different times, promptly relieved by injections of 40 mg papaverin sulphate A third time patient had attack at home, and called a physician, who gave her an injection of morphin Patient was made "sleepy," but relief was not as prompt as from papaverin

CASE 14—M E, outside case White man, 46 years of age Myocardial insufficiency Dyspnea and preeordial pain relieved temporarily by injection of 40 mg papaverin sulphate

CASE 15—M B, outside case White woman, 64 years of age Anginal pains and dyspnea from myocardial and arteriosclerotic changes Relieved temporarily by injection of 40 mg papaverin sulphate Pulse distinctly fuller and pressure lower after injection

CASE 16—M H, outside case White woman, 26 years of age Acute neuritis of right hand and forearm No relief from papaverin injection of 40 mg

CASE 17—Dr F P, 56 years of age Renal colic, very severe, requiring chloroform inhalations and morphin Slight relief experienced for an hour or two after injection of 40 mg papaverin sulphate

CASE 18—R G, dispensary case, F 23824 White man, 32 years of age Lead colic Distinct relief from injection of 40 mg papaverin sulphate Pulse before injection 80, after injection 72 per minute

CASE 19—N J, outside case Man, black, 40 years of age Acute enteritis Pain was relieved by injecting 40 mg of papaverin sulphate He came next day asking for another injection

CASE 20—M K, outside case White woman, 38 years of age Severe nervous headache, relieved by injecting 40 mg of papaverin sulphate

CASE 21—M K, outside case White woman, 30 years of age Acute vesical spasm Pain relieved very quickly by injection of 40 mg of papaverin sulphate

CASE 22—M B, outside case White man, 56 years of age Anginoid attacks Relieved by 40 mg of papaverin hydrochlorid in solution by mouth every four hours

CASE 23—M S, outside case White man, 60 years of age Cardiac dyspnea, very bad Very little relief from injection of 40 mg papaverin

CASE 24—J W, Ward F (care of Dr F A Evans) Hysteria Injection of 40 mg papaverin sulphate for nervousness and insomnia, not efficacious

CASE 25—S W, Ward O (care of Dr F A Evans) Hyperacidity and gallstones (?) Injection of 40 mg papaverin sulphate for a paroxysm of pain brought about complete relief in fifteen minutes Before injection respiration 24, pulse 84, blood pressure, systolic 165, diastolic 95, after injection respiration 26, pulse 70, blood pressure, systolic 140, diastolic 90

CASE 26—J W, Ward F (care of Dr F A Evans) Psychasthenia malignum, hysteria Injection of 40 mg papaverin sulphate for nervousness and insomnia proved efficacious, slept all night Before injection respiration 24, pulse 88, half hour after injection respiration 24, pulse 84

CASE 27—A B, Ward F (care of Dr F A Evans) Syphilis of aorta, aortic insufficiency, myocardial insufficiency Injection of 40 mg papaverin sulphate for dyspnea and restlessness Quieted a little after administration, slept brokenly several hours Before injection respiration 30, pulse 80, half hour after injection respiration 30, pulse 80

CASE 28—E M, Ward F (care of Dr F A Evans) Hypertension, myocardial failure Injection of 40 mg papaverin sulphate for dyspnea and restlessness Quite efficacious, patient almost asleep in ten minutes Before injection respiration 32, pulse 94, blood pressure, systolic 185, diastolic 100, after injection respiration 26, pulse 93, blood pressure, systolic 185, diastolic 95

CASE 29—T H, Ward F (care of Dr F A Evans) Lobar pneumonia, pericarditis Injection of 40 mg papaverin sulphate not efficacious in relieving pleural pain Neither is relief given by injection of  $\frac{1}{4}$  grain morphin

CASE 30—J D, Ward F (care of Dr F A Evans) Aortic insufficiency; bronchopneumonia Injected 40 mg papaverin sulphate for relief of cough, dyspnea and restlessness Quite efficacious, asleep in thirty-five minutes and slept five hours Before injection respiration 28, pulse 100, after injection respiration 24, pulse 98

CASE 31—G G, Ward F (care of Dr F A Evans) Pneumonia, pneumothorax Injected 40 mg papaverin sulphate to induce quiet sleep Not asleep in half hour, but quiet and drowsy Before injection respiration 30, pulse 128, after injection respiration 30, pulse 112

CASE 32—R A, Ward O (care of Dr F A Evans) Bronchopneumonia Injection of papaverin sulphate for dyspnea and restlessness Not efficacious, some infiltration at site of injection next day

#### SUMMARY

From the above data, it will be seen that the alkaloid papaverin exhibits certain very interesting pharmacologic properties Chief among these are its effect on the heart and blood pressure, its action on the coronary circulation, its stimulating effect on the respiration, its relaxing and tonus-lowering influence on the smooth muscle structures, and its considerable analgesic power

These, together with its comparatively low toxicity, suggested its employment for therapeutic purposes The clinical experiences described speak in its favor, and it is hoped that further observations may be made to determine its exact therapeutic value in medicine

# A CLINICAL HEMOGLOBINOMETER

HERBERT HAESSLER

AND

HARRY S NEWCOMER, M D

PHILADELPHIA

We have devised a colorimeter for the clinical estimation of hemoglobin which possesses several advantages over instruments now in use. Those methods for the estimation of color density, which depend upon the comparison of a sample with an interrupted series of standards, have always been the most satisfactory. The eye is able to place a sample with more certainty between two members of a variable series than it is to compare a sample with a uniformly graded scale. The latter only becomes accurate when the error is absorbed into a great number of readings, and as yet there had been no instrument devised superior to the Fleischl-Miescher for such a procedure. For a single operation, comparison with a series offers much more certainty as to the correctness of the choice.

We have adopted the principle of the Sahli hemoglobinometer, modifying it to satisfy the above concepts. The Sahli instrument has the advantage that it offers a comparison color of the same material as the sample, and a color to whose shade variations the eye is particularly sensitive. It has the disadvantage of uncertainty of comparison, due to the fact that one cannot reconsider a discarded choice. Therefore, instead of the single standard tube, we use eleven comparison tubes, whose densities correspond to readings varying by 10 from 10 per cent to 110 per cent hemoglobin. The standard fluids are made up according to Sahli's specifications. The tube marked 100 per cent contains in 10,100 c c the equivalent in hematin hydrochlorid of 17.2 gm of hemoglobin. Sahli bases his percentage readings on blood containing 17.2 gm hemoglobin per 100 c c. Such a blood, diluted 1 to 100, would then correspond exactly with the mixture in our 100 per cent tube.

Our procedure for the preparation of the standards is as follows. Ten c c of human blood are drawn from a vein into a certified pipet and immediately emptied into and rinsed in 100 c c of 10th normal hydrochloric acid. At the same time, from the same vein, 2 c c of blood are drawn into a 2 c c pipette and emptied into and rinsed in 400 c c of 1 per cent sodium carbonate solution. This latter solution

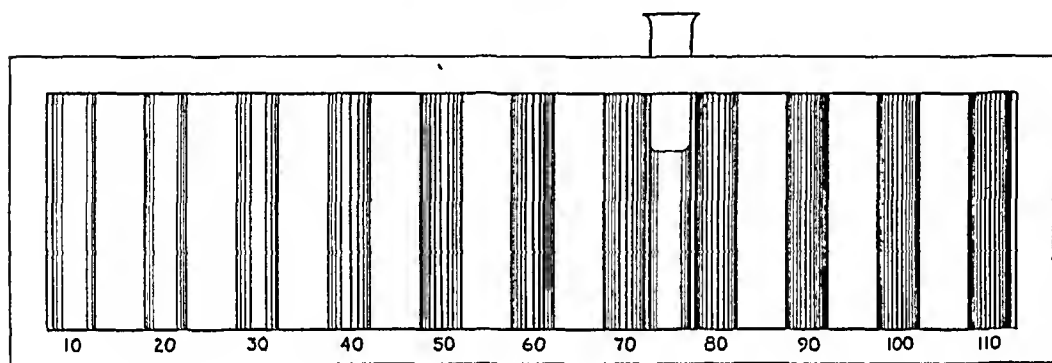
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\* Submitted for publication, April 1, 1916

\* From the Ayer Clinical Laboratory of the Pennsylvania Hospital

is then calibrated on a Fleischl-Miescher hemoglobinometer and the hemoglobin of the blood determined in grams per 100 c c. The hydrochloric acid mixture is then made up with tenth-normal hydrochloric acid in dilutions corresponding to 17.2 gm hemoglobin per 10,100 c c of fluid for the 100 per cent tube and fractions of that for the other tubes.

The hematin hydrochlorid is insoluble and forms a fine suspension. This settles easily. For that reason beads are enclosed in the tubes so that the fluid can easily be made homogeneous by a little shaking. It is impossible to seal the tubes off short above the fluid. A very satisfactory and simple method is to partially close them and then seal with a plug of paraffin dropped in from a pipet. Experiment showed that the eye can most readily compare colors in the form of vertical rectangles, and the size and shape eventually used seems to be the most favorable one. The tubes are made from glass tubing which to the eye



Hemoglobinometer with comparison tube containing a test specimen in the rack but not at the correct reading, scale six-tenths natural size

has a uniform thickness and whose outside diameter (about 7 mm) does not vary by more than one-tenth mm. Such tubing is easy to pick out of ordinary stock.

The tubes are conveniently arranged in a rack, so that the comparison tube can be slipped in between any two of them. The frame measures  $5\frac{1}{2}$  by 18 cm. It is of red vulcanized fiber, which is cheaper and more durable than gutta-percha, and the color of which does not seem to be objectionable. Septa between the tubes and opal glass behind them have been tried and discarded. The simpler construction facilitates the reading. Reflected light obtained by placing the instrument on a sheet of paper, as is done in ordinary titration, is best suited for the readings.

On placing the comparison tube in the rack, a malposition immediately strikes the eye as producing a sharp discontinuity, as is shown by the accompanying illustration of the instrument. On moving the tube one way or the other in the rack the point at which the shading



becomes harmonious is readily found and the amount of deviation from one of the multiples of ten estimated

The dilution of the patient's blood can well be done with an ordinary red blood pipet, using tenth-normal hydrochloric acid as a diluting fluid. A dilution of 1 to 100 is made. The red blood pipet will deliver enough fluid to fill the comparison chamber, and it offers a convenient and accurate instrument for the purpose with the additional advantage that it is usually already available or readily obtainable.

The readings can be made in any light and with certainty to a multiple of 5 or in other words to within  $2\frac{1}{2}$  of the correct percentage.

The frame is also very convenient when made up to use as a phenol-sulphonephthalein colorimeter. For this purpose, however, it will never be as satisfactory as those instruments in which the standard solution can be made up each time fresh with a specimen of the urine as a diluent.

# THE USE OF THE "KARELL CURE" IN THE TREATMENT OF CARDIAC, RENAL AND HEPATIC DROPSIES \*

EDWARD HARRIS GOODMAN, M D

PHILADELPHIA

The various measures recommended for the successful treatment of failing cardiac, renal and hepatic functions, with their concurrent edema of more or less severity, are legion, and one would be unwise to undertake the treatment of such conditions without a full appreciation of the value of each. Drugs, physical therapeutics and diet form the triad upon which reliance is usually placed, and generally speaking, in the lay as well as in the professional mind the greatest of these is drugs. There are many dropsical cases in the treatment of which one must use all three, there are many in which physical measures may be safely dispensed with, and there are many cases of severe renal and cardiac breakdown in which drugs as well as physical measures may be disregarded, but there are none in which diet has not earned a well-deserved and fixed place.

It may be stated without fear of serious criticism, that the majority of cardiac dropsies and a large proportion of dropsies of renal origin will improve with the combination of rest in bed and an appropriate diet. The diet which has served me best and which I have employed successfully for some time is that known as the Karell diet, or the Karell cure. Although half a century has elapsed since Karell published his paper (1866), this particular form of diet bearing his name seems to be but little known and but rarely used. In Germany it is slowly finding its place, but as recently as 1908 Jacobs<sup>1</sup> wrote that he could find no mention of it in the textbooks, and but little practical knowledge of its existence among physicians. In America it is known but not intimately, and it has not secured for it the acclaim which would be its portion were it employed more frequently.

During my association with Dr. John H. Musser in the Presbyterian and University hospitals, and with Dr. James E. Talley in the former institution, I have been given the opportunity to make free use of this method of treatment during the past few years, and have employed this diet in many cases, between a hundred and a hundred and fifty approximately. This experience, which has been productive of

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\* Read before the College of Physicians Philadelphia April 5 1916

<sup>1</sup> Jacobs Munchen med Wchnschr 1908 14 839

improvement in the majority of these patients, is the *raison d'être* of this paper

The technic of the Karell cure is simple and easily carried out as far as the physician is concerned. The patient receives daily at 8 a m, 12 m, 4 p m, and 8 p m 200 cc of raw or boiled milk, warm or cold, according to taste. No other food or liquid should be given. This strict diet sometimes, nay, many times, meets with violent opposition from the patient, and great complaint is made because of thirst. Thirst is particularly tormenting during the first three or four days of the "cure," and often it becomes necessary to allow the patient to rinse out his mouth with water, instructing him to swallow none, however. Hunger is not so common a complaint, but when urgent, a small piece of dry toast or zwieback may be given with each portion of milk. During the first few days the patient requires continual encouragement to persist with the treatment, but the moral effect of the rapid loss of weight, as shown by daily weighings, together with the very evident decrease of the edema, prove sufficient argument to him, and no further complaint is heard. Just how long this very strict diet is to be continued depends on the rapidity with which edema diminishes and on the patient's plea for more food. Usually the diet may be increased at the end of a week's time by giving a soft-boiled egg, without salt or pepper, at 10 a m, and a piece of zwieback at 6 p m. The next day an egg may be given at 10 a m and at 2 p m, with a piece of white bread, and from now on food is gradually increased until a full diet is being taken. During this time the daily quantum of liquid should not exceed 800 cc, and this fluid should be in the form of milk, until the patient receives a full diet, when the milk may be discontinued and cocoa or tea substituted, the amount of liquid remaining the same, however. No more than 800 cc of fluid should be taken for from two to four weeks after the disappearance of edema.

The "full diet" spoken of above is a misnomer, for the diet should be salt poor, and the following foods comprise this dietary: meat, fresh-water fish, cream soups, fresh eggs cooked in any form or raw, rice, corn, hominy, Indian corn, endives, peas, string beans, French beans, artichokes, onions, leeks, carrots, salads except lettuce, cauliflower, potatoes, cereals of all kinds, butter unsalted, bread without salt, sweet-meats, sugar, chocolates, cocoa, tea, coffee, fruits, milk, cream cheese and Swiss cheese, puddings, junket, ice-cream.

During the "cure," which it seems needless to say must be carried out with the patient in bed, the bowels must be kept open, and for this purpose laxatives in pill form are preferable to salines, merely because they require no water for their administration. In a typical case, that is, in those individuals who begin to lose weight through the loss of edema, and who show increased diuresis, no other medication is

required, but where improvement is not seen at the end of three days, or when symptoms are urgent, such as dyspnea, oppression, restlessness, unduly frequent and weak pulse, or active uremic signs, the drugs and other measures usually indicated in such conditions should be used. This question will be further discussed later on.

The article by Karell<sup>2</sup> in which he described his milk cure was published in 1866 and apparently was entirely forgotten, and would no doubt have remained in obscurity, had not Jacob<sup>1</sup> reported the results obtained with it in Lenhartz clinic, where it had been used for about fifteen years. Just how many of the few writers on the subject have read Karell's original paper it is impossible to say, but Jacob has given the year of publication as 1868 instead of 1866, and his error has found its way into practically every article since 1908, so that the inference that few have read the original is perhaps justified. Possessed as it is of great practical interest and of historical interest as well, written in a peculiarly intimate manner and naive in spirit, Karell's paper should be read at first hand, but I can not forbear quoting at length from this very interesting article. He writes

It is always with a rich profusion of remedies and with the greatest confidence in their efficacy that the medical youth enters upon the practical exercise of his profession. However, experience does not long delay in demonstrating the inanity of that pretended richness, the circle of medicines prescribed narrows year by year and the physician whose age has ripened talent finally finds himself obliged to confess that the surface of his finger nail would be large enough upon which to inscribe the names of the medicines used in practice.

If I confess to something of the same nature, if at the end of thirty-four years of practice a sort of skepticism takes possession of my spirit, relative to the curative virtue of many medicaments, I have, on the other hand, gained faith in the efficacy of certain means whose object is to change and to modify nutrition.

If I call attention today to the methodical cure by means of milk, I do it in the firm conviction that the number of cures brought about by this treatment is due, in large part, to the judicious use and to the strict observance of the method. It is only thus that truly startling results have been obtained, results which the general public have qualified as marvelous.

It may be objected that milk as a remedy is fairly well known and that every physician uses it according to the exigency of the case. I confess that all physicians are sufficiently informed regarding the virtue of milk, as food and as antidote, but I speak from experience when I say that in general the milk cure scrupulously administered in amounts rigorously fixed is not sufficiently, or but rarely, recognized by practitioners as an heroic and sovereign remedy.

Karell, who was physician to the Emperor of Russia, indulges in reminiscences of his excursion with the monarch through Russia, and speaks of his pleasure in seeing the milk cure being used extensively in many cases. He then transcribes a letter from the famous Niemeyer, which is worthy of being again transcribed. After having communi-

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<sup>2</sup> Karell. *Arch. gen. de med.*, 1866, viii, 513.

cated to the Tübingen professor his experiences, he received the following letter some time later

I am infinitely grateful to you for having recommended the milk cure, I have used it so often and extol it in such a way that it would make you smile. If one were sincere enough to recognize that there exists a very large number of disease whose cause should not be sought in disturbances of certain organs but rather in a perverse state of nutrition, of which we know neither the extent nor the nature, he would believe in the curative virtue of milk, and would regard it as a true scientific advance that one can find in that article of food a harmless measure and at the same time so efficacious in changing completely the state of nutrition.

Karell has used the milk cure in at least 200 cases and found that it gave good results where other measures proved to be valueless. As to the principle underlying its virtues, he declines to give any opinion and thus he defends by claiming "The art of healing would surely remain sterile if one should limit himself only to those remedies whose effects can be controlled even to the smallest detail." The diseases which are treated best by the cure are particularly dropsical conditions, but he gives a large list of other diseases of more or less chronic nature.

The writer has restricted himself to the employment of the Karell cure in cases of renal, cardiac and hepatic edema, and it is only these diseases which will be discussed in this paper, although other clinicians have used it in bronchitis, emphysema, gastric and intestinal conditions, and particularly in the treatment of obesity. Edema, from whatever cause is the condition, is par excellence the disease in which the most notable results are achieved, however.

#### ILLUSTRATIVE CASES

The following cases will illustrate the effect of the Karell cure in cases of edema.

CASE 1—John A., aged 70, white, was admitted to the hospital Feb. 11, 1914, complaining of dyspnea and edema of feet. A diagnosis of endocarditis and arteriosclerosis was made.

The patient states that he was fairly well until three years ago, when he became dyspneic and his feet began to swell. Since this time dyspnea has been pronounced on exertion, he has marked palpitation of the heart.

Examination revealed a well-nourished man, heart enlarged to right and to left, systolic murmur at apex and at aortic cartilage, extra systoles, vessels sclerotic, legs greatly swollen.

The urine had a specific gravity of 1.020, showed a trace of albumin, but no casts, blood hemoglobin, 75 per cent, leukocytes, 10,850, red blood cells, 4,970,000, blood pressure, systolic 212, diastolic 148.

Under treatment the patient regained fairly good condition and was discharged March 4, 1914. Edema had disappeared entirely, the subjective symptoms had much improved, and there was some reduction in blood pressure.

CASE 2—Frank P., aged 38, was admitted to the hospital Nov. 7, 1913, complaining of cardiac palpitation, dyspnea and edema of legs and scrotum. A diagnosis was made of aortic insufficiency and intermittent heart block.

The patient was well until two months ago, when, on returning home from work, he suddenly became very dyspneic. Similar attacks were of frequent occurrence after this.

It was learned that the patient had contracted syphilis and Neisserian infection at 28 years of age. He was treated in the Presbyterian Hospital two weeks ago for conditions similar to the present illness.

Examination showed him to be a poorly nourished man. Marked pallor and cyanosis were present and dyspnea pronounced, edema of legs and genitalia. Heart, apex beat was in the sixth interspace, 2 cm. outside left midclavicular line, right border at right parasternal line, left border 3 cm. to left of left midclavicular line. A systolic thrill was felt at the apex, apex beat fluttering and diffuse. A presystolic murmur was heard at the apex, followed by a short diastolic murmur, double murmur at aortic and pulmonary cartilages. The liver was palpable. The lower extremities were edematous, as were also the penis and scrotum. The pulse was irregular and rapid, and the arteries sclerosed. While he was in the ward he had an attack of typical Stokes-Adams syndrome.

The urine had a specific gravity of 1.015, was cloudy, showed albumin, but no casts.

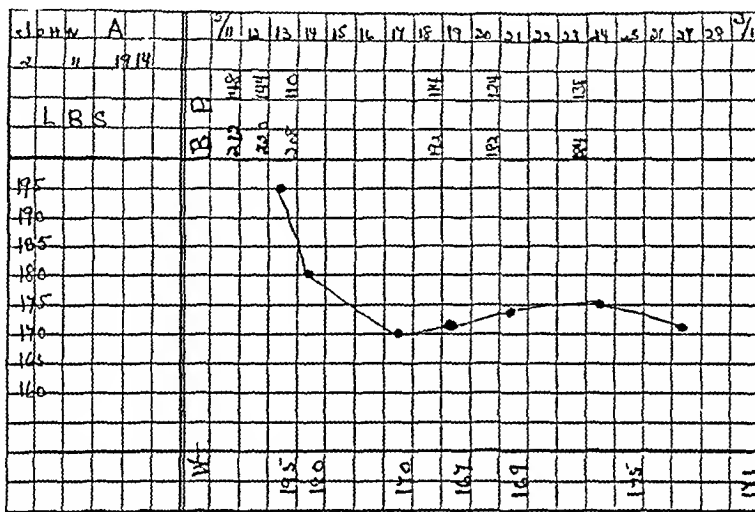


Fig. 1 (Case of John A.)—Line with heavy dots indicates loss of body weight, amounting to 26 pounds in ten days.

Blood hemoglobin, 58 per cent, red blood corpuscles 3,280,000, leukocytes 6,400, blood pressure, systolic 205, diastolic, 115.

Under treatment the patient lost in weight 8 pounds in seventeen days. Nine days after beginning Karell cure edema had almost entirely disappeared, and there had been a loss of weight of 15 pounds. Subjective symptoms had improved, and there were no sharp attacks of dyspnea, such as were complained of on admission, although patient was still dyspneic. The heart was more regular, pulse less frequent, no change in blood pressure. The patient was discharged Nov. 28, 1913, much improved.

Figure 2 shows loss of weight only, as the urine was not saved quantitatively and therefore is not recorded. Prognosis in this case was grave, although there was benefit from the Karell cure. The patient returned Dec. 29, 1913, with symptoms similar to those on his previous admissions. The Karell cure was again prescribed, but there was no improvement. Cardiac stimulants were employed, but patient succumbed Jan. 6, 1914.

CASE 3—Frederick P., aged 63, the same patient discussed in Case 4, was readmitted to the hospital Nov. 30, 1915. He had been coming since his discharge to my dispensary, but the exertion proved to be too much and ten days

after his discharge dyspnea became marked, and legs, penis and scrotum became edematous. The condition on admission was the same as was given in Case 2, and a diagnosis of cardiac renal disease was made.

Under treatment the loss of weight amounted to 22 pounds in thirteen days. There was again disappearance of all edema and great improvement in subjective symptoms.

Figure 3 merely shows loss of weight. No accurate record was kept of the amount of urine, as the patient stipulated before entering the hospital the second time that he should be allowed to go to the toilet room, so the urine could not be collected quantitatively, as was possible during the patient's first visit to the hospital.

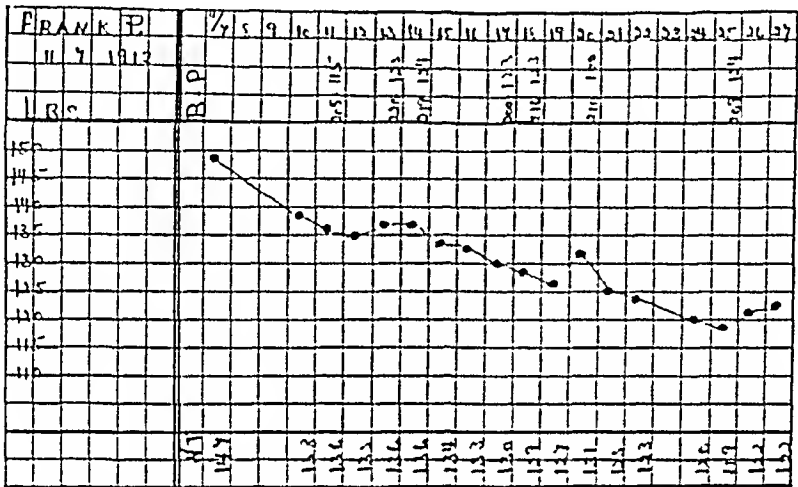


Fig 2 (Case of Frank P) —Line with heavy dots indicates the loss of body weight, amounting to 18 pounds in seventeen days

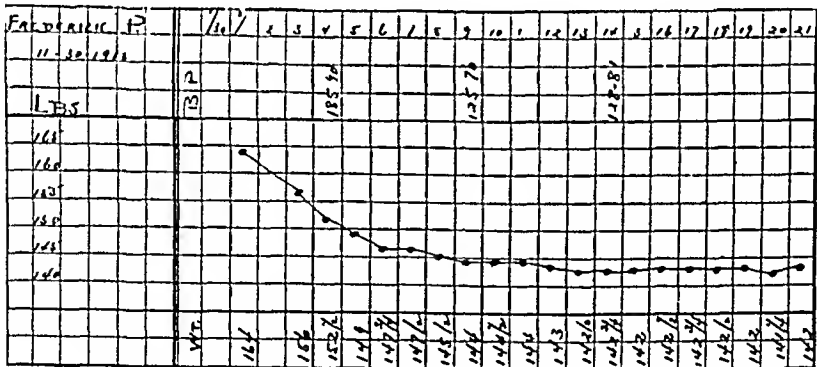


Fig 3 (Case of Frederick P) —Line with heavy dots indicates loss of body weight, amounting to 22 pounds in thirteen days

CASE 4—Frederick P, aged 63, was admitted to the hospital Oct 9, 1915, complaining of retention of urine and shortness of breath.

For two months the patient had had a smothering feeling at night, causing him to awaken with a start. It was observed that he became dyspneic on the slightest exertion and when walking he had to stop and rest after going the distance of a few hundred feet. He has had no polyuria and no other symptoms worth noting, except that after Sept 3, 1915, a month previous to admission, he had become very weak.

He had been a sufferer from asthma previously, and a year ago he had a nasal operation which failed to furnish relief. His other history was negative.

Examination showed the patient to be a well-built man, complexion pasty, dorsal decubitus, but the slightest exertion causes dyspnea, face edematous, some hydrothorax both sides. The heart apex was in the sixth interspace to left of the midclavicular line. There was marked pulsation in the fourth and fifth left intercostal spaces. The right border was 4 cm to right of midsternal line, left border 15 cm to left of midsternal line. There was no murmur at apex, and the sounds were weak. The second sound at pulmonary and aortic cartilages was accentuated. There was marked edema of the entire body, and the abdomen showed ascites. The legs, scrotum and penis were very edematous, arteries sclerotic, catheterization required, eye grounds negative.

The urine was 1013, albumin a faint trace, with hyaline and granular casts, phenolsulphonaphthalein, 7 per cent.

Blood Hemoglobin, 84 (?) per cent, red blood corpuscles, 2,450,000 (?), leukocytes, 5,350, blood pressure systolic, 169, diastolic, 110.

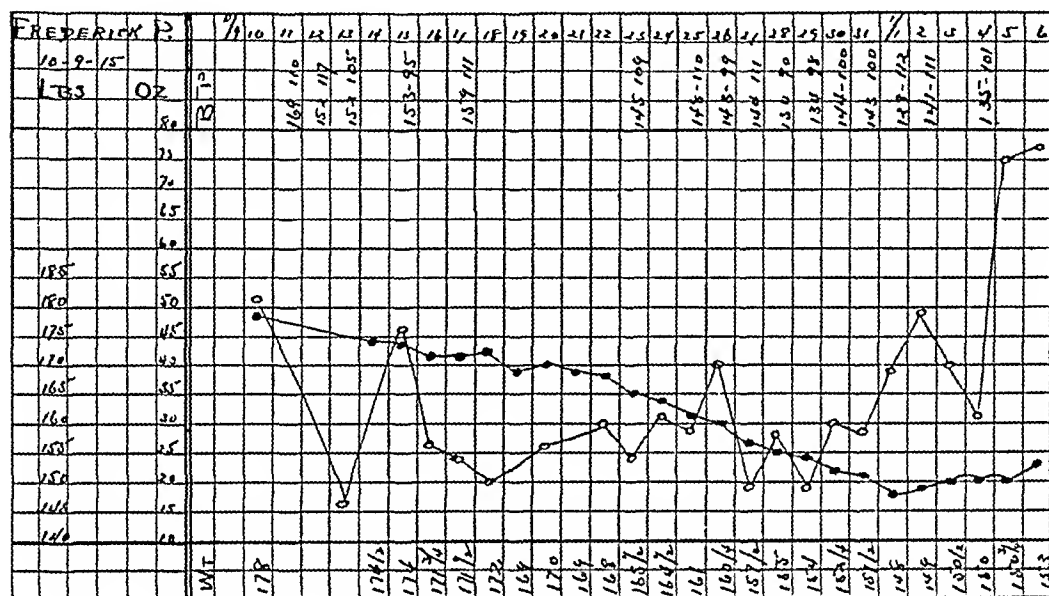


Fig 4—Same patient whose record is illustrated in Figure 3. The line with heavy dots indicates loss of body weight, line with open dots indicates amount of urine secreted, which rapidly increased at first, and then fell off, providing an indication for other therapeutic measures.

Under treatment there was a disappearance of the edema, and an improvement of subjective symptoms. The loss of weight was gradual, but amounted to 30 pounds in thirty days. There was a reduction of blood pressure. In this case hot packs were used and caffeine 0.36 gm a day. The patient was discharged Nov 6, 1915.

Figure 4 shows marked increase in the amount of urine with later a falling off in quantity. On October 12 because of this, hot packs and caffeine were ordered, later, digitalis, 2 cc of the tincture daily.

CASE 5—Ferdinand S, white, aged 61, was admitted to the hospital Jan 12, 1914, complaining of dyspnea and swelling of the lower extremities. His case was diagnosed as cardiorenal.

His illness had begun six months before with shortness of breath, dizziness, and swelling of the feet and legs. Thereafter these symptoms had become intensified, until the patient could scarcely get his breath when he made even the



slightest exertion His previous medical history showed pneumoma ten years before, and acute articular rheumatism two years before

Examination showed a well-nourished man with marked dyspnea There was chronic passive congestion at the base of the lungs The heart sounds weak but regular, with no murmurs, and slight enlargement to the left Ascites was present, the liver was palpable, and the lower extremities were edematous

The urine was 1029, with a trace of albumin, and with a few hyaline and granular casts at times

Blood Hemoglobin, 70 per cent, red blood corpuscles, 4,800,000, leukocytes, 7,950, blood pressure systolic, 190, diastolic, 140

Under treatment there was a fall in body weight, and gradual increase in diuresis Until Jan 19, 1914, patient felt no better, but at this time he was improved, and the blood pressure, body weight and edema were all diminished The patient was discharged Feb 10, 1914, much improved

Figure 5 shows the drop in body weight, the sudden diuresis, followed by a fall The urine was not accurately measured for forty-eight hours, January 16 and 17 Then there was again an increase in amount and a gradual fall in blood pressure

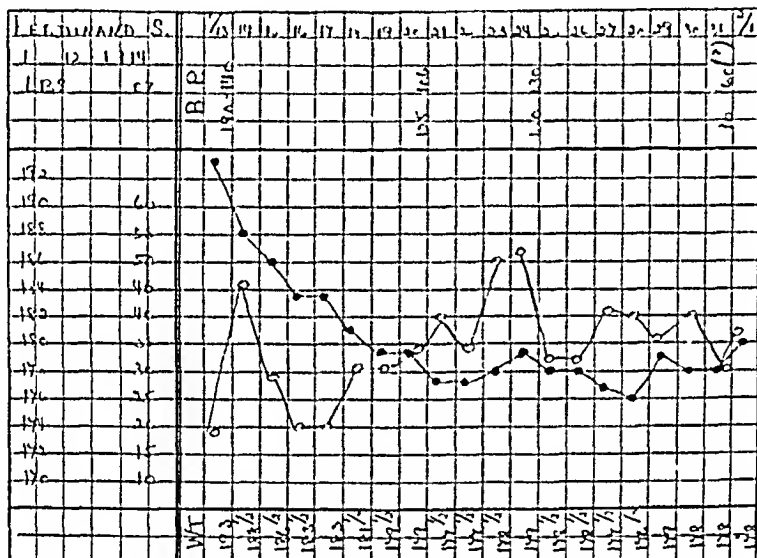


Fig 5 (Case of Ferdinand S) —Line with heavy dots indicates loss of body weight, which was 16 pounds in eight days, line with open dots, increase of diuresis

CASE 6—Benedict P, aged 28, was admitted to the hospital July 10, 1913, complaining of dyspnea, distention of abdomen, edema of legs His trouble was diagnosed as chronic nephritis

His illness had begun six months before, when the patient noticed that his feet were swollen and he was unable to walk without becoming much fatigued Two weeks before entrance edema became worse and dyspnea appeared

Examination showed nutrition good There were anasarca, ascites, and edema of the lungs The heart apex was in the fifth midclavicular line, right border indefinite, left border in left midclavicular line The sounds were indistinct, and there were no murmurs There was no enlargement of the spleen or liver The eye grounds were negative

The urine was 1018, heavy cloud albumin, and hyaline and granular casts, phenolsulphonaphthalein 18 per cent

Blood Hemoglobin, 53 per cent, red blood cells, 2,680,000, leukocytes, 9,900, blood pressure systolic, 129, diastolic, 80

Under treatment there was a loss of weight of 26 pounds in fourteen days. There was slight increase in urine excretion, and the edema became much less, although it was not entirely gone on discharge. There was a disappearance of all subjective symptoms, and a marked increase in chlorid output. The patient was discharged Aug 27, 1913, much improved.

Figure 6 is designed to show loss of weight and delayed diuresis.

CASE 7—Mary S., aged 57, was admitted to the hospital Oct 7, 1914, complaining of shortness of breath, swelling of the legs and distention of the abdomen. A diagnosis of cardiorenal disease was made.

The patient had been suffering with edema of the legs for about a year or more, but she had become worse about five weeks before entrance to the hospital. The trouble had begun with abdominal distention, then dyspnea appeared, which became so pronounced that she could not lie down. She had been forced to sleep in her chair. Palpitation of the heart was marked, and there was blood-tinged expectoration.

The previous medical history showed rheumatism at the age of 16.

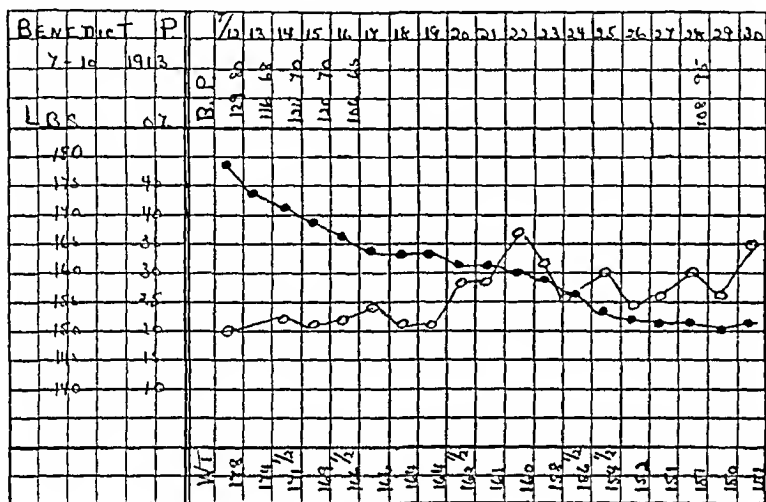


Fig 6 (Case of Benedict P) —Line with heavy dots shows loss of body weight, amounting to 26 pounds in fourteen days, line with open dots shows increase of diuresis, which was delayed in this case.

Examination showed the patient to be fairly well nourished, but very edematous. Pallor was present. The heart was irregular, and there was enlargement to the left and to the right, with a systolic murmur at the base. The arteries were sclerotic. The liver was palpable, and there were ascites, and marked edema of legs.

The urine was 1016, with a trace of albumin and with hyaline and granular casts.

Blood Hemoglobin 60 per cent, red blood cells, 3,640,000, leukocytes 7,600, blood pressure systolic, 145, diastolic, 90.

Under treatment there was a disappearance of all edema and a loss of weight of 54 pounds in ten days. The blood pressure was reduced from 145 systolic and 90 diastolic to 125 systolic and 80 diastolic in seven days.

Figure 7 shows the rapid loss of weight and the great diuresis, amounting to 4,500 cc. On the second day of treatment the urine was 100 ounces, on third day 148 ounces, fourth day 138 ounces, fifth day 145, or a total of almost 16 liters (15,940 cc) in five days.

CASE 8—Edward R., aged 35, was admitted to the hospital Jan 12, 1914, complaining of "asthma," dyspnea, and swelling of the feet, legs and abdomen. The case was diagnosed as hepatic cirrhosis.

The patient had had shortness of breath for a number of years, but during the past six weeks he had been worse, and at the time of entrance was forced to rest sitting up. Cough had become very troublesome.

With the exception of asthma, patient had never been sick, but had been in the University Hospital in 1905 for some gastric trouble. He had always taken alcohol to excess, admitted Neisserian infection but denied syphilis.

Examination showed the patient to be a large, well-built man, semirecumbent decubitus. The breathing was labored and wheezing. There was pallor, and the lungs were emphysematous, with sibilant râles. The apex heart beat was not visible, the sounds were weak, and there was a soft systolic murmur at the apex. The area was not enlarged. There was abdominal ascites. The liver was palpable, and there was edema of feet and legs.

The urine was negative, phenolsulphonephthalein, 66 per cent. Gastric analysis showed total acid 8, free hydrochloric acid 0. Stools revealed occult blood present.

Blood Hemoglobin, 45 per cent, red blood cells, 3,390,000, leukocytes, 10,600, blood pressure systolic, 120, diastolic, 70.

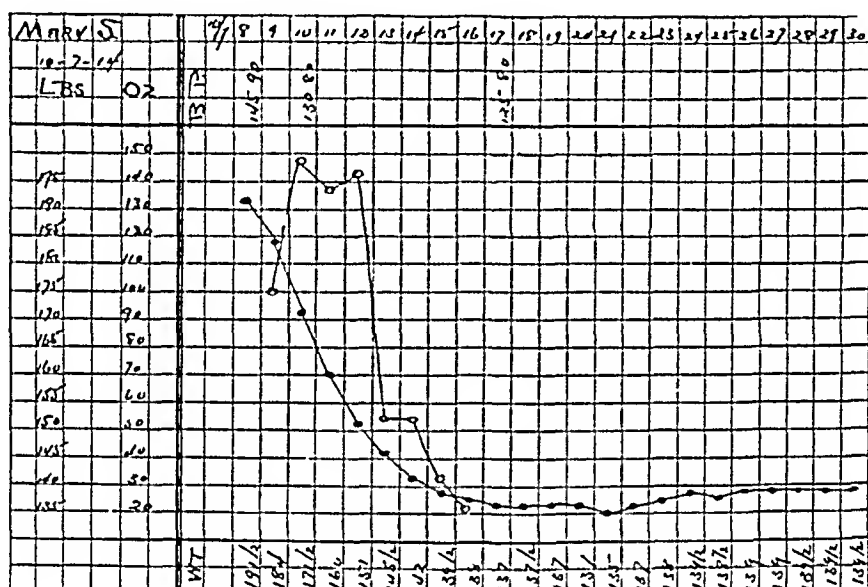


Fig 7 (Case of Mary S) —Line with heavy dots shows loss of body weight, which was 54 pounds in ten days, line with open dots shows rapid increase of diuresis, 531 ounces of urine being secreted in four days.

Treatment produced a loss of weight of 39 pounds in sixteen days. The diet was increased on the seventh day of treatment. The patient was improved when discharged, Feb 26, 1914.

Figure 8 shows a rapid loss of weight and a prompt increase in the amount of urine.

CASE 9—William W, aged 22, was admitted to the hospital Nov 4, 1913 complaining of dyspnea, cough and expectoration, pain on inspiration, scanty urination, swelling of feet, and ascites. The case was diagnosed as endocarditis, decompensation.

The patient had never been sick with a similar illness. He had been apparently well and walking about until two weeks before admittance, when he began to notice swelling of the feet, and began to lose his appetite. He also developed a severe pain in the right infraclavicular region, sharp, stabbing in character, made worse by taking a deep breath, and on coughing, which soon developed. He became dyspneic on exertion. For the past two weeks

he had been passing but little urine, which was dark in color. There was pain in back over the renal region. The face had started to swell about two weeks previously, and about that time he noticed that his abdomen had become swollen.

His previous medical history was negative. He was in the habit of using alcohol to excess and of doing hard work.

Examination showed a well-nourished young man. He had a uremic odor to the breath, face swollen and flushed, dyspneic. The abdomen was swollen, the lungs tuberculous, with pleural effusion. The apex heart beat was in the sixth interspace, 14 cm to the left of the midsternal line, upper border at the third rib, right border 4½ cm, left border 14 cm from midsternum. The sounds were irregular, gallop rhythm, systolic murmur at the apex. The abdomen showed ascites. The liver was palpable and pulsating. The lower and upper extremities were edematous.

The urine was 1080 with heavy cloud albumin and no casts.

Blood. Red blood cells, 4,710,000, leukocytes, 18,150, blood pressure systolic, 131, diastolic, 93.

As a result of treatment, on November 10 the patient seemed a little better, was not so dyspneic, but began to be jaundiced. Later, Nov 19, 1913, there was parentesis thoracis. Patient gradually became worse and despite active use of cardiac stimulants, succumbed on Nov 28, 1913.

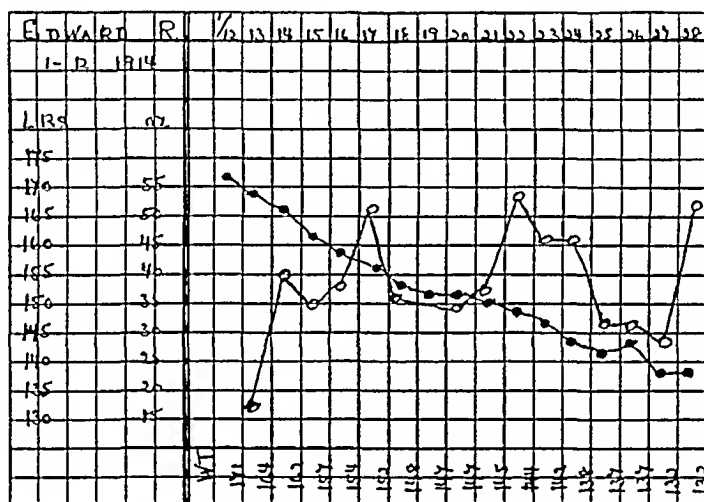


Fig 8 (Case of Edward R.)—Shows effect of the milk diet in a case of hepatic cirrhosis. The line with heavy dots indicates the loss of body weight, which was 39 pounds in sixteen days, line with open dots shows the increase in diuresis.

Figure 9 shows only moderate loss of weight very slowly achieved, with urine amounts continually low. There was no improvement in pulse rate. The prognosis on admission was guarded.

CASE 10—James K., aged 49, white, was admitted to the hospital Sept 2, 1913, complaining of swelling of legs, genitalia and abdomen. A diagnosis of chronic nephritis was made.

The patient had been well until five weeks before, when he noticed that he was beginning to tire easily, had general malaise and was losing appetite. One week before he had first observed swelling in the face, and the next day general swelling throughout the body. He had had diarrhea one week before, soreness across the abdomen, pain in the back and polyuria. Three weeks before he had had pains about the heart which had lasted for three days and prevented him from taking full breath. Dyspnea and palpitation also were complained of.

He had had nephritis with dropsy eighteen years before, and had been treated in the Presbyterian Hospital and discharged as cured

Examination showed a well-nourished man There was slight cyanosis, the face was puffy and the breath urinous A few moist râles could be detected at the base of both lungs The right border of the heart was 2 cm, the left border 12 cm to the left of the midsternal line The upper border

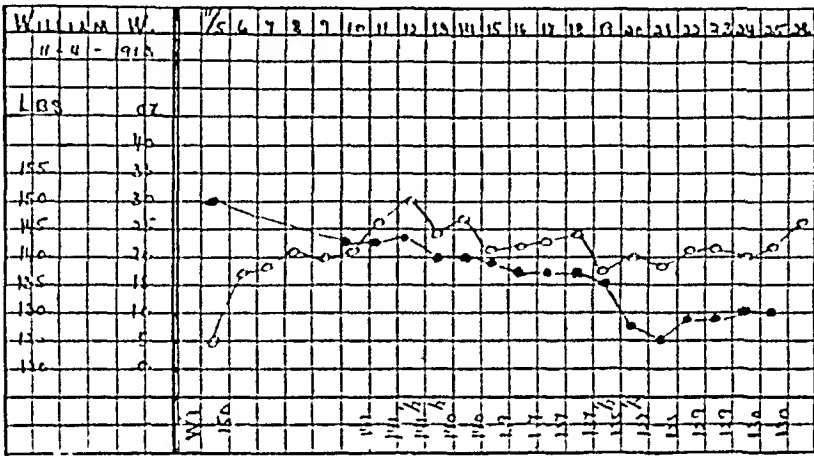


Fig 9 (Case of William W) —Illustrates failure of the Karell cure, slow and halting loss of body weight indicated by the line with heavy dots, and very small amounts of urine, indicated by the line with open dots, the largest amount being but 30 ounces

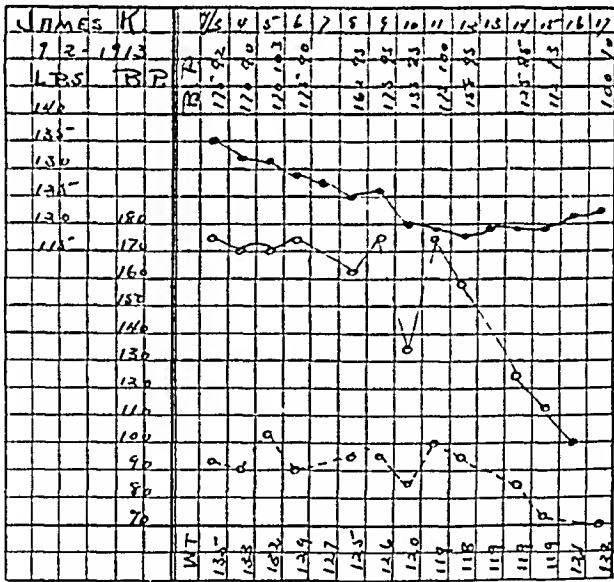


Fig 10 (Case of James K) —Shows chiefly the lowering of blood pressure, both systolic and diastolic, due to Karell diet Line with heavy dots indicates loss of body weight, solid line with open dots indicates the systolic blood pressure, and broken line with open dots, diastolic blood pressure

was at the third rib The first sound at the mitral area was roughened and prolonged The pulse was regular The arteries were sclerotic, the urine showed many hyaline casts, and edema was general

The urine was 1010, with a heavy cloud albumin and many hyaline casts, and phenolsulphonephthalein excretion of 40 per cent

Blood hemoglobin, 60 per cent, red blood cells, 4,570,000, leukocytes, 11,200, blood pressure systolic, 175, diastolic, 92

Under treatment there was a loss of 16 pounds of edema in eight days, with disappearance of all swelling. Diuresis increased, but it has not been charted as the amount was not accurately measured. There was a gradual fall in blood pressure, systolic and diastolic, and a disappearance of all subjective symptoms. The patient was discharged Sept 17, 1913, much improved.

Figure 10 is designed to show the loss of weight and decrease of blood pressure.

CASE 11—Margaret McC, aged 37, was admitted to the hospital Feb 23, 1910, complaining of edema of face, abdomen, extremities, and of pains in the back. Her trouble was diagnosed as nephritis.

Two weeks before she had noticed puffiness about the eyes, most marked in the mornings. In a few days her feet had become swollen, and later her hands. The swelling had increased each day, and finally the abdomen had become involved in the edematous process.

Her previous medical history showed that she had had scarlet fever.

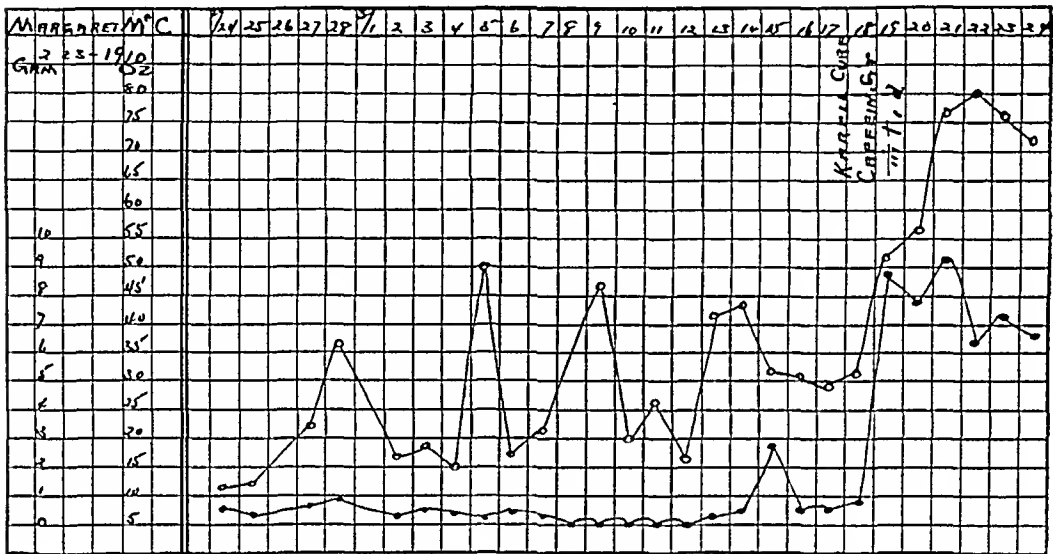


Fig 11 (Case of Margaret McC) —Shows retention of chlorids on a solid salt-poor diet, prompt elimination of chlorids and increased diuresis on Karell cure, with caffeine and hot packs. Line with heavy dots indicates body weight, line with open dots shows the effect of the Karell treatment on diuresis.

Examination revealed slight edema of the face, heart enlarged to the left, with a soft, low-pitched systolic murmur at the apex. No ascites. Extremities edematous.

The urine was 1016, with a small amount of albumin and few fine granular and hyaline casts.

The blood pressure was 125 systolic and 100 diastolic.

In the treatment salt-free diet was used, but not the Karell cure. On January 19, owing to signs of impending uremia, a Karell diet with hot packs and caffeine 0.2 gm three times a day were ordered, and the result was improvement in the urine, the chlorids and in the patient's general condition.

Figure 11 shows absolute chlorid retention despite increasing amount of urine, and the prompt and rapid elimination of chlorids and marked diuresis on combination Karell diet and medication.

CASE 12—Elizabeth W, aged 36, was admitted to the hospital Feb 12, 1910, complaining of edema of extremities and abdomen. Her case was diagnosed as nephritis.

Three weeks before, the patient had noticed slight swelling in the feet at night, the edema disappearing by morning, and puffiness about the eyes had appeared at the same time. The swelling had gradually increased, the entire body had become edematous. During the summer of 1909 the patient had noticed some swelling in her feet which disappeared in a few days.

Examination showed anasarca, heart not enlarged, accentuation of both pulmonic and aortic second sounds and no retinitis.

The urine was 1013, with large amounts of albumin and hyaline and granular casts.

Under treatment there was a rapid loss of weight and disappearance of edema. The patient was discharged much improved.

Figure 12 illustrates the great loss in body weight, increase in urine, and marked chlorid elimination.

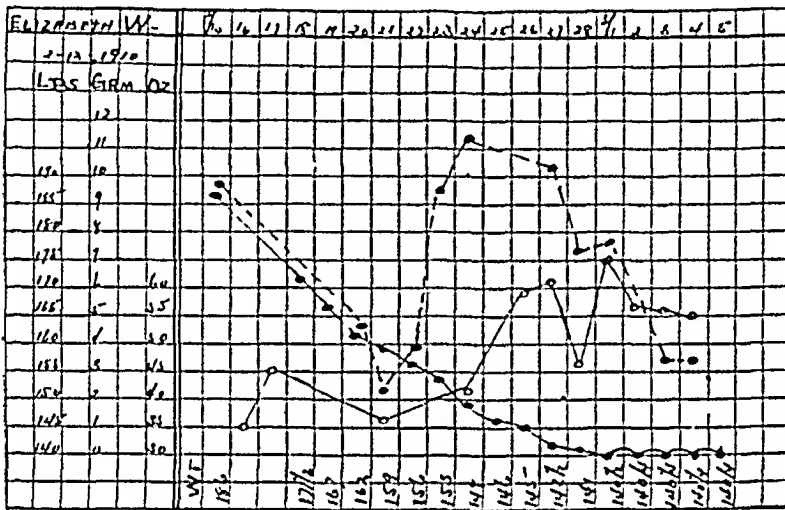


Fig 12 (Case of Elizabeth W) —Solid line with heavy dots indicates loss of body weight, which was 30 pounds in fourteen days. Broken line with heavy dots shows the elimination of chlorids, and the line with open dots the increase of urine excretion.

#### EFFECT OF THE CURE

1 *Subjective State*—The most important feature of the cure is that it gives the human organism the minimum of work. All strain on the heart is removed as far as is possible by the rest in bed and by the very small amount of food given at frequent intervals, which yet furnishes enough nutrition under the circumstances and provides fuel in such a form that it can be utilized with the least possible effort. The good effects are seen by the patient almost before they are noted by the physician. The patient rests easier, there is a gradual cessation of subjective symptoms, headache, depression, vertigo, and there is a return of the desire to partake of food where formerly nausea and vomiting held sway. There is an improvement in the respiratory condition, and the patient has less dyspnea, requires fewer pillows for his comfort, gradually assumes the prone position, and is able to have long sleep without the intervention of morphin. These favorable changes are the reward of the strict observance of the Karel cure,

and the strict observance consists in giving only 200 c c of milk at 8 a m, 12 m, 4 p m, and 8 p m. The purpose of the treatment is immediately defeated if more fluid is permitted or if the patient is allowed to drink the milk whenever he pleases.

2 *Heart*—The effect on the heart is soon noticed apart from the subjective symptoms of restored compensation. Good effects are seen more constantly in those cases which are best termed myodegeneration cordis, that type of cardiac disease seen in senility, emphysema, chronic alcoholism and in cachectic states (Wittich). In 60 per cent of this type of case improvement is seen. Valvular disease is improved in about 43 per cent of cases, arteriosclerosis in 33 per cent, and according to Wittich, in nephritis only 14 per cent, a percentage below that seen in my cases. Under the combination of rest in bed and the Karel diet the pulse assumes, first, a better quality, and later becomes less irregular and less frequent. These effects are seen in many cases in which no medication is used, although we do not presume to deny the place digitalis preparations have earned for themselves in the treatment of arrhythmia and allorhythmia. In some cases digitalis preparations must be used, but their action is materially reinforced by the use of the milk cure.

3 *Blood pressure* is generally lowered, particularly in cases of renal hypertension, as may be seen from Figure 10.

4 *Urine*—When the daily quantity of urine is closely watched it will be seen that there is marked increase in the amount. This in some cases begins within the first few days and reaches its height during the first week (Fig 7), but in other cases diuresis is delayed (Figs 4 and 12). Most authors state that the largest amounts are seen in the first two to three days, but this has not been the rule in my cases. At times there is a delayed diuresis, as has been described by His. The urine passed in twenty-four hours may be two or three times the amount of milk ingested, 5 liters having been observed. In the case of Mary S. (Case 7), almost 4,500 c c were voided, and in this patient there was a loss of weight of 54 pounds in ten days. The specific gravity of the urine is variable, but generally speaking, it is in inverse ratio to the amount of urine excreted. On the other hand, there has been noted a distinct rise in specific gravity without any change in the amount. The quantity of albumin diminishes and disappears when there is chronic passive congestion, and there is also a reduction in the number of casts, although this is not so apparent when a true nephritis is present. The effect on the phenolsulphonephthalein output is variable, but it can not be said that there is any marked increase in the amount excreted.

5 *The chlorid output* is generally very much increased over the intake. Repeated analyses by Hegler have given the percentage of



salt in milk as 0.14, which would be about 1.1 gm in 800 c c milk. By reference to Figure 12 it may be seen what relation the output bears to the intake. Wittich regards this negative chlorid balance as a good indication of the efficacy of the treatment, and attaches greater importance to it than to the twenty-four-hour quantity of urine in estimating the changes in the circulatory apparatus. Ordinarily there is a marked increase in the amount of sodium chlorid during the first few days, both as to percentage and total amount. After two or three days the percentage falls, but the total amount increases, with the increase in urine, and finally, as the urine amount returns to normal, the chlorid balance is regained (Wittich).

#### IO WHAT IS IMPROVEMENT DUE?

An attempt has been made to ascribe the benefits following the Karell cure to three factors, namely, reduction in the amount of fluid, the minimum of salt contained in the milk, and finally to the melting of body protein. The last-named factor has probably some bearing on the effect of the cure when carried out in obese patients, but is scarcely to be considered as a factor in the cases of edema in which as much as 31 pounds have been lost in three days (Mary S., Fig. 7). Hence, in the cases studied as a basis for this paper the so-called melting of body protein hardly calls for consideration.

Metabolic studies have been made by Hegler on patients suffering with renal or cardiac decompensation or both, associated with obesity. He does not consider that the limited amount of fluid ingested alone accounts for the diuresis and loss of weight, and this he proves by a patient who took 800 c c of milk and a liter of infusion of lime tree blossoms, and who nevertheless lost 10 kg weight in eight days.

To the low salt content of the diet has been ascribed much of the benefit resulting from the cure. During the first three or four days of the cure patients excrete daily 8, 10 or 15 gm, or even more, of sodium chlorid, but after from five to eight days the excretion of this salt sinks to from 1 to 2 gm per day and when a diet containing from 1 to 3 gm of sodium chlorid is given, there is a transitory tendency to sodium chlorid retention. If the sodium chlorid equilibrium is followed for a longer period of time, there is always a preponderance of sodium chlorid excreted over that ingested, as much as from 40 to 60 gm in from three to four weeks. This is in contradistinction to Hedinger, who found a considerable sodium chlorid retention and water retention, which, to his mind, accounted for the rapid gain in weight after completion of the cure (obese cases?). Hegler has made the interesting observation that sodium chlorid added to the diet of an obesity case causes no water retention and no gain in weight, but when the same experiment is tried in dropsical individuals, there is an immediate cessa-

tion of loss in weight, with water and sodium chlorid retention, and finally gain in weight. This latter experiment is by no means new, however, and was first performed by Javal and Widal. Somewhat similar results were also obtained by v. Hoesslin in normal individuals.

From this it would seem that the good effects might be ascribed to the sodium chlorid poverty of the diet, but here again we find contradiction in a case described by Wittich.

TABLE 1—SHOWING DIURESIS AND SODIUM CHLORID OUTPUT AS AFFECTED BY KARELL TREATMENT (WITTICH'S PATIENT)

Date, 1911	Diet	Urine	Sodium Chlorid in Grams	
			Intake	Output
May 28	Salt free diet without limiting fluid	700	3	4.2
May 29	Salt free diet without limiting fluid	700	3	3.5
May 30	Karell cure	1,400	17	10.1
May 31	Karell cure	1,300	17	9.2
June 1	Karell cure	800	17	4.4

Wittich's patient, as shown in Table 1, received for two days a salt-poor diet, but was allowed as much fluid as he desired. There was no increase in diuresis, however, but as soon as the Karell diet was given, although now but 800 c c of fluid was permitted, the amount of urine was doubled. It is difficult to see just how a reduction of sodium chlorid intake (13 gm. less than on the salt-poor diet) could account for the increase in urine and the remarkable increase in the amount of sodium chlorid excretion.

It appears more probable that there are several factors which account for the efficiency of the Karell diet: (1) absolute rest in bed, which removes from the organism practically all work, and decreases the amount of work to be borne by the heart, (2) the low amount of fluid and food (800 c c, containing only 27 gm. protein and furnishing about 520 calories) also limits the amount of cardiac effort, (3) the low amount of sodium chlorid, and finally (4) the effect of the Karell cure may be due to either the salt-poor diet or to the low amount of fluid, or it may be the sum of the two, which brings about the brilliant results.

Hegler, as a result of his metabolic studies, decides that the value of the Karell cure can not be judged from such studies, but must be estimated from the clinical side, and I would here call attention to Karell's remark previously quoted. No matter to what factor or factors the good results are ascribed the fact remains that in dropsical

conditions of renal, cardiac and perhaps hepatic origin the Karell milk diet, given as taught by Karell, is the diet par excellence

#### THE USE OF DRUGS IN COMBINATION WITH THE KARELL CURE

In pursuing my studies the object has been to use only the Karell cure itself and to avoid as far as possible any medication. In many cases the milk diet alone brings about the desired improvement and no drugs are necessary, but in other cases medicines can not be dispensed with. It has been noted frequently that patients who have been treated for a period of time with digitalis preparations without much improvement do particularly well on the Karell diet alone. On the other hand, cases presenting marked dyspnea, cyanosis, a frequent and irregular pulse, need relief more rapidly than is possible with the Karell cure by itself. Such drugs as camphor, digitalis, strophanthus, caffeine and morphin should be used in such emergencies, but it will be found unnecessary in the majority of cases to continue with their administration for any great length of time. Generally at the expiration of twenty-four or forty-eight hours there has been such a marked improvement that they may be discontinued.

When the Karell cure has been used for a few days, and when there has been no objective improvement, that is, when the quantity of urine becomes markedly decreased, when there is no change in the character of the pulse, and when the body weight and the edema remain as before, or when both increase, then drugs must be used. Of these, digitalis, theocin, caffeine and strophanthin seem to be especially suitable, and an observation of Jacob's is worthy of repetition, namely, that whereas in these cases digitalis preparations alone, even in large doses, have had but little effect on the decompensated heart, when used with the Karell cure a much better result is seen and much smaller doses of digitalis are required. This is especially to be seen when digitalis has been discontinued for a few days before beginning again with their administration.

#### PROGNOSTIC SIGNIFICANCE OF THE KARELL CURE

Jacob, Wittich and others have called attention to the prognostic significance to the pure Karell cure, or the Karell cure used without medication. Wittich especially regards the prognosis as serious when there is chlorid equilibrium, persistence of edema, and stationary urinary output or a diminution of the same, but particularly important is the chlorid output, by means of which one is enabled to decide on the prognosis by the first day. A positive chlorid balance is absolutely unfavorable, and in his case this was seen in but two cases, and these patients died within the first few days of the cure. Wittich also claims to see in the chlorid metabolism not only an index of the extent

of reestablished compensation, but also of beginning compensation following a Karell cure. When at the end of a Karell cure there begins to be salt retention, he regards this as an early sign of a fresh decompensatory state—a preedematous stage of cardiac decompensation—and he recommends a repetition of the Karell cure in order to spare the heart any further fatigue.

In 1910 I called attention to the unfavorable significance of this chlorid retention, and a chart published at that time is reproduced here (Fig 11). This patient was not on the Karell diet, but was given what is popularly called a salt-free diet, but more properly, a salt-poor diet.

#### CONTRAINDICATIONS

During our experiences with the Karell cure there have been no bad results when the treatment has been properly used. There are cases, however, which do not seem to respond to the diet, and for this reason the Karell treatment is no longer recommended in these instances. Patients exhibiting symptoms of uremia should not be put on the Karell cure, which restricts the fluid intake to a minimum, as it has been shown by Senator and others that in this crisis the fluid intake should be greatly augmented for the purpose of flooding from the system the unknown toxic substance or substances believed to be the causative factor in uremia. Wittich states that the Karell cure in two cases of uremia left him absolutely in the lurch, and the patients were made materially worse. The treatment of such individuals should be that well known to all practitioners of medicine, and the Karell cure has no place whatever in the management of such cases.

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## ON THE REACTION OF THE CEREBROSPINAL FLUID

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In its mode of origin and in its pathways of absorption as well as in its physical and chemical properties, the cerebrospinal fluid is unique among the body fluids. Two facts derived from clinical and experimental observations have been established within recent years with a fair degree of conclusiveness, namely, the dual origin of the cerebrospinal fluid and its return to the general circulation chiefly by a process of filtration through the arachnoid villi into the great sinuses<sup>1, 2</sup>. Unlike the circulating lymph, which is derived from the blood by a process of filtration, diffusion and osmosis, the cerebrospinal fluid is the secretory product of the ependymal cells which cover the choroid plexuses, although it must be admitted that certain fundamental anatomic and physiologic aspects of this problem are still unsolved.

Another interesting observation which has been brought forth by a number of workers is that these plexuses constitute a remarkably effective barrier against the entry into the cerebrospinal fluid of substances present in the circulating blood. This observation may indeed explain, in part at least, the unique physical and chemical properties of the fluid, for in these respects also it is unlike any other fluid in the body, being approached in its composition most nearly by the sweat, tears, and aqueous humor of the eye. From the circulating lymph normal cerebrospinal fluid differs in several striking particulars: it is of lower specific gravity, contains a small content of salt, only minute traces of protein, and no fibrinogen.

Concerning the reaction of the cerebrospinal fluid, little more definite is known beyond the general statement of most authors that it is alkaline. As to the degree of this alkalinity in comparison to the other body fluids and more especially to the blood little is known. According to Cavazzani—and most authors quote him—the alkalinity of the fluid is only half as great as that of the blood<sup>2, 3</sup>. Mott has attempted to express the degrees of reaction in terms of percentages of

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\* From the George Williams Hooper Foundation for Medical Research, and the Neurologic Clinic, the University of California Medical School, San Francisco

1 Weed, Lewis H. Jour Med Research, 1914, xxvi, 21, 51, 93

2 Mott, F W. Lancet, London, 1910, ii, 1, 79

3 Plaut, F, Rehm, O, and Schottmuller, H. Leitfaden zur Untersuchung der Cerebrospinalflussigkeit, Jena, Gustav Fischer, 1913, pp 16, 23

sodium hydroxid. Calculated in this way, the reaction has been found by him to vary only slightly in different animals, and in man in different pathologic conditions. On an average it corresponds to 0.1 per cent sodium hydroxid.

That such titrimetric determinations of reaction lack accuracy has been repeatedly emphasized in recent literature<sup>4, 5</sup>. The more extensive knowledge gained from modern physicochemical studies has shown that the titrimetric method in its present form is inaccurate, and that an exact knowledge of the reaction of a solution can be gained only from a determination of its hydrogen ion concentration.

Although extensive studies have been made of the hydrogen ion concentration of most biologic fluids, electrometrically or by the colorimetric method, we were surprised to find almost no mention in the literature of similar determinations on the cerebrospinal fluid. Neither Sørensen<sup>6</sup> nor Michaelis<sup>7</sup> in their exhaustive treatises on this subject make any reference to such studies.

So far as we are aware, Polanyi, quoted by Bisgaard,<sup>8</sup> was the first to determine the hydrogen ion concentration of the spinal fluid. He found the value for pH to be 10.04 ( $9.08 \times 10^{-11}$ ). Bisgaard, however, who carried out similar determinations both by the gas-chain electrometric method, as well as colorimetrically, gives the value as 8.10, although fluids obtained post mortem were found by him to be more alkaline (pH=8.46 to 9.25). This worker found also that the results obtained by the Hasselbach apparatus corresponded well with those obtained colorimetrically with phenolphthalein as indicator.

In view of the meagerness of data on this point, it seemed worthwhile to determine the hydrogen ion concentration of normal cerebrospinal fluid, as well as of fluid obtained from patients suffering from several types of disease. In the present paper we wish to report the results of such determinations made by the colorimetric method upon forty-seven fluids.

#### METHOD

*Sources of Error*—In a recent communication<sup>9</sup> we presented in some detail the principles and the extent of applicability of the colorimetric method for determining the hydrogen ion concentration of bio-

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4 Clark, W. M. Jour Infect Dis 1915, vii, 109.

5 Hurwitz, S. H., Meyer, K. F., and Ostenberg, Z. Bull Johns Hopkins Hosp, 1916, xxviii, 16.

6 Sørensen, S. P. L., Ergeb d Physiol, 1912, vii, 393.

7 Michaelis, Leonor. Die Wasserstoffionenkonzentration, Berlin Julius Springer, 1914.

8 Bisgaard, A. Biochem Ztschr 1913-1914, lvi, 1.

logic fluids, but only brief reference was then made to the sources of error of the method. These in the main are three in number,<sup>9</sup> and a critical analysis of them will show that they do not materially alter the accuracy of the method in its application to cerebrospinal fluid.

1 The Effect of Coloring Matter in Biologic Fluids. One of the greatest obstacles met with in the use of colorimetry in the determination of the ionization of biologic fluids is the turbidity and the pigment present in the majority of such fluids. In the case of blood this difficulty was unsurmountable until Levy, Rowntree and Marriott<sup>10</sup> suggested the method of determining the ionization of the dialysate obtained by dialyzing blood through collodion membranes for a given time interval. It is obvious that this difficulty does not arise in the case of cerebrospinal fluid, which, in health and when carefully obtained without contamination with blood, is usually a colorless, limpid fluid. Should any turbidity exist due to the presence of inflammatory products, the fluid can still be read directly by use of the comparator method described in a previous paper.

2 Influence of Neutral Salts. Those who have used this method are agreed that the presence of neutral salts in sufficient concentration greatly influences the point at which a given indicator changes color. In this respect various indicators show different degrees of sensitiveness. In most instances the neutral salt concentration must be two to three times that of blood in order to render the use of indicators for these determinations subject to gross error.<sup>11</sup> From the available analyses of the blood and the cerebrospinal fluid it would appear, how-

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9 A source of error which should be mentioned, but which is not peculiar to any one method, is that which may result from the loss of carbon dioxide in determinations of hydrogen ion concentration on carbon-dioxide-containing fluids, such as blood and cerebrospinal fluid. The possibility of this error has been precluded in electrometric measurements by the use of a special electrode, the Hasselbach electrode, for the purpose of keeping the carbon dioxide tension at a constant level during the measurements. In the use of the colorimetric method this difficulty cannot be met with entire satisfaction, and the values for pH obtained do not in a strict sense have the absolute accuracy possessed by readings made with the hydrogen electrode. But it would appear from Mott's work<sup>2</sup> that the carbon dioxide in cerebrospinal fluid is in more stable combination than in blood, and for this reason this medium is more suited to colorimetric readings than is the blood. In every case it is important to make the determinations on perfectly fresh specimens and with a similar technic in order to give the results comparative value.

10 Levy, R. L., Rowntree, L. G., and Marriott, W. McKim. *THE ARCHIVES INT. MED.*, 1915, *xvi*, 389.

11 Rona, P. *Handbuch d. Biochemische Arbeitsmethoden*, E. Abderhalden, 1911, *v*, 321.

ever, that the inorganic salts exist in the two fluids in about equal concentration<sup>12</sup>

3 Influence of Proteins and their Split Products Because of their colloidal properties and their amphoteric character, proteins or their split products greatly modify the point at which certain indicators change color, and this quite independently of the hydrogen ion concentration Their presence, therefore, constitutes a source of error which at times is sufficiently great to render the colorimetric method inapplicable to solutions containing protein in high concentration From what has already been said concerning the extremely low protein content of normal cerebrospinal fluid, it is apparent that this source of error does not apply to it According to Mott and others, normal cerebrospinal fluid contains only 0.03 per cent of protein, and in pathologic cases it seldom exceeds 0.25 per cent<sup>3</sup>

From the above considerations it is clear that because of the unique chemical composition of the cerebrospinal fluid colorimetric determinations of its ionization are not subject to the same sources of error which would arise in the case of other biologic fluids

*Technic*—The principles of the colorimetric method, the preparation of the standard comparison tubes and the manner of expressing the results are recorded in recent communications<sup>5, 10</sup> In this paper it is necessary only to give the several steps in the procedure

Spinal fluid is obtained by lumbar puncture in the usual way, and is received into thoroughly clean and dry Jena glass test tubes<sup>13</sup> Because of the clear, watery nature of the fluid and its low protein content, it is possible to make the determinations of the hydrogen ion concentration either directly or indirectly by testing the dialysate as recommended for blood by Levy, Rowntree, and Marriott

For a direct reading 3 c.c. of spinal fluid are delivered into a small clean and dry test tube 10 by 100 mm., and 0.3 c.c. of a 0.01 per cent solution of phenolsulphonephthalein is added After inverting the test tube several times in order to distribute the color evenly, comparisons are made between the color obtained and those of a series of standard

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12 Gautier and Zdarek (quoted by C. E. Simon, *Clinical Diagnosis*, Ed. 8, Philadelphia, Lea & Febiger, 1914, p. 501) give the concentration of chlorids, phosphates and sulphates in cerebrospinal fluid as 6.44 per mille, while Hammarsten, O. (*A Text Book of Physiological Chemistry*, Ed. 8, New York, John Wiley & Sons, 1909, p. 239) states that the blood as a whole contains in ordinary cases from 770 to 820 per mille water, with from 180 to 230 per mille solids, of which from 6 to 10 per mille are inorganic and the remainder organic solids

13 We have found that some of the thick-walled test tubes, even when thoroughly clean, deliver up alkali in sufficient amount to render distilled water placed in them alkaline to phenolsulphonephthalein This source of error must of course be obviated



Ol Case	Date	Sex	Age	Number	Initial	Count		Value of pH	Value of pH	Diagnosis, Value of pH		
1	8/17/15	S	R	55	Tuberculosis of wrist	15113	B — S F —	3	0	0	8.3	8.8
2	8/19/15	A	H	50	Diabetes	16238	B — S F —	2	0	0	8.25	8.15
3	8/19/15	A	G	63	Chronic nephritis	16593	B — S F —	2	0	0	8.3	8.2
4	8/24/15	C	B	39	Purpura	16599	B — S F —	1	0	0	9.3	8.15
5	8/24/15	J	G	28	Sinusitis	12102	B — S F —	2	0	0	8.3	8.15
6	8/24/15 8/28/15	H	V	7	Cerebral injury, decompression	House 9732	B — S F —	2	0	0	8.15 8.3	8.0 8.15
7	8/26/15	P	P	53	Pulmonary tuberculosis	11107	B — S F —	2	0	0	8.3	8.1
8	8/31/15	W	H	53	Cerebral injury	House 9732	B — S F —	2	0	0	8.15	8.05
9	9/ 1/15	D	S	56	Neurasthenia	11116	B — S F —	0	0	0	8.25	8.2
10	9/ 1/15	T	W	45	Tubercles (?)	17108	B — S F —	5	0	0	8.3	8.1
11	9/21/15	J	S	43	"Dizziness"	17175	B — S F —	3	0	0	8.3	8.15
12	9/30/15	J	S	51	History of syphilis	17578	B — S F —	2	0	0	8.25	8.0
13	9/30/15	O	D	45	Retinitis	17651	B — S F —	2	0	0	8.3	7.95
14	10/ 2/15	M	L	20	History of syphilis in infection (?)	17915	B — S F —	1	0	0	8.25	8.05
15	10/ 7/15	T	L	28	Papillitis	17765	B — S F —	0	0	0	8.3	8.25
16	10/ 7/15	A	B	42	Tubercles (?)		B — S F —	0	0	0		8.25
17	10/19/15	L	I	42	Syphilis (?)	18178	B — S F —	0	0	0	8.3	8.0
18	10/23/15	A	A	45	Tubercles (?)	10283	B — S F —	1	0	0	8.25	
19	12/ 8/15	T	B	43	Syphilis (?)	19291	B — S F —	0	0	0	9.20	8.0
												7.65

solutions consisting of phosphate mixtures prepared according to the directions of Sorensen<sup>14</sup> The color in the standard series which most closely matches that of the solution tested gives the hydrogen ion concentration of the test fluid

If it be desired to test the dialysate in order to compare its hydrogen ion concentration with the dialysate of the blood of the same patient, 1 to 2 c c of cerebrospinal fluid are placed into a collodion sac, which is then lowered into a small test tube containing 3 c c of physiologic salt solution, until the fluid on the outside of the sac is as high as that on the inside Dialysis is allowed to continue for five minutes The collodion sac is then removed, and 0.3 c c of the indicator solution is added to the dialysate Color comparisons with the standard scale are now made as detailed above For comparative purposes the same quantity of the same patient's blood is tested in a similar manner

#### RESULTS

*The Reaction of Normal Cerebrospinal Fluid*—In Table 1 have been grouped nineteen normal patients in whom the reaction of the cerebrospinal fluid was determined These patients, as will appear, represent a large variety of clinical conditions, and in a strict sense cannot be classed as normal But so far as the cytologic, chemical and serum tests indicate, no abnormality existed in the central nervous system, and on this ground it is justifiable to place them in the normal group

It will be noted that in the nineteen determinations made upon the fluid directly the average value of the hydrogen ion exponent (pH) was 8.26, with a minimum value of 8.15 and a maximum value of 8.3, whereas the average of the same number of readings made on the dialysate was slightly lower, pH being equal to 8.11 Of interest also is the fact that the two lowest readings were obtained in cases of cerebral injury, treated by decompression and the withdrawal by puncture of considerable amounts of fluid It is not unlikely that the diminished alkalinity in these instances may have been due to dilution of the fluid by hypersecretion

As compared with the hydrogen ion concentration of the dialysate of the cerebrospinal fluid, that of the blood obtained from the same patient was found to be much higher In the six instances in the normal group in which the blood was also tested an average value for pH of 7.66 was obtained Thus the hydrogen ion concentration of the blood in these cases was greater than that of the spinal fluid by the value of 0.45

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14 The standard test solutions were prepared for us by Hynson Westcott and Company Baltimore

In connection with the reaction of the cerebrospinal fluid in health, there are several interesting physiologic problems which still await solution. One of these concerns the relationship between the normal functional activity of the nervous centers and the reaction of the fluid. Mott<sup>2</sup> proposes the view that after normal sleep the alkalinity may be slightly greater than at the end of a day's work, because of the production of acid substances resulting from nerve cell activity.

TABLE 2—A COMPARISON OF THE HYDROGEN ION CONCENTRATION OF BLOOD AND CEREBROSPINAL FLUID

No. of Case	Reaction of Cerebrospinal Fluid Value of pH	Reaction of Cerebrospinal Fluid Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH
9	8.25	8.2	7.7
10	8.3	8.1	7.6
11	8.3	8.15	7.75
12	8.25	8.0	7.65
14	8.25	8.05	7.65
19	8.2	8.0	7.65
22	8.3	8.15	7.75
23	8.3	8.15	7.6
25	7.95	7.9	7.65
27	8.35	8.15	7.7
28	8.3	8.1	7.65
29	8.3	8.1	7.65
32	8.3	8.15	7.5
40	8.2	8.1	7.7
42	8.15	8.15	7.75
43	7.95	7.75	7.65
46	8.4	8.15	7.75
17	8.3	7.95	7.60
Average		8.07	7.66

Another problem of interest concerns the reaction of the cerebrospinal fluid in different loci. From the work of a number of observers it is now known that ventricular and subarachnoid fluids may differ in some important respects. It has been shown, for instance, that there is a slightly higher percentage of sugar in ventricular than in subarachnoid fluid, whereas the reverse is true of the albumin content, furthermore, that ventricular fluid may be richer in waste substances which may have been added to it during its passage through the sub-

arachnoid perivascular and perineuronal spaces<sup>15</sup> The possibility may therefore be entertained that the two fluids, which differ in these marked particulars, may also show measurable differences in reaction

*The Reaction of Cerebrospinal Fluid and of Blood Compared*—In a previous paragraph it was pointed out that blood and spinal fluid obtained from the same patient at the same time may show a considerable difference in the hydrogen ion concentration as determined by the colorimetric method In Table 2 are given eighteen instances in which such comparative data were obtained The average value of the hydrogen ion concentration tested upon the dialysate of the spinal fluid was 8.07 as compared with 7.66 obtained in the case of the blood dialysate Thus the ionization of blood tested in this way is greater than that of cerebrospinal fluid by the value of 0.41 It must be emphasized, however, that the need of resorting to dialysis doubtless introduces a source of error in the data given, for the reason that the two fluids dialyzed—blood and cerebrospinal fluid—are not chemically equivalent, the former containing a higher percentage of protein and colloids, both of which are known to influence the dispersion of electrolytes through porous membranes<sup>16</sup> These considerations, however, do not affect the observation that the hydrogen ion concentration of the spinal fluid tested directly is lower than that of the blood<sup>17</sup>

*The Reaction of the Cerebrospinal Fluid in Disease*—In this paper the observations have been limited to those diseases in which lumbar puncture is ordinarily done as a routine measure either for diagnosis or treatment Tables 3 and 4 include twenty-eight cases of syphilitic disease and of syphilitic affections of the nervous system in which the reaction of the spinal fluid was determined The diagnosis in all of these patients was confirmed either by cytologic and chemical tests or by the routine Wassermann reaction of the blood and spinal fluid

From an examination of Table 3 it will be noted that the average hydrogen ion concentration (pH) of the spinal fluid in primary and secondary cases of syphilis is equal to 8.26, while determinations of the dialysate give somewhat lower readings (pH=8.14) Similar readings made upon the dialysate of the blood in seven of these patients gave an average value of pH equal to 7.64, which is 0.5 lower than that obtained for the dialysate of the spinal fluid By comparing these figures with those recorded in Table 1, it will be observed that these values do not differ widely from those obtained for normal fluids The

15 Cushing, H Jour Med Research, 1914, XXXI, 12, 13, 15

16 Ostwald, W A Handbook of Colloid Chemistry, Philadelphia, P Blakiston's Sons, 1915, p 219

17 The hydrogen ion concentration of the blood determined by the hydrogen electrode averages  $0.3 \times 10^{-7}$ , or pH=7.5 The value for pH\* obtained by the colorimetric method is 7.66

TABLE 3- GEN ION CONCENTRATION OF THE CEREBROSPINAL FLUID IN SYPHILITIC DISEASE

Number of Case	Date	Name	Age	Diagnosis	Hospital Number	Wassermann*	Cell Count	Nonne	Noguchi	Reaction of Cerebrospinal Fluid, Value of pH	Reaction of Spinal Fluid, Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH
20	8/24/15	L S	53	Syphilis	6276	B + + S F -	1	0	0	8.3	8.15	
21	8/26/15	A L	30	Syphilis, epilepsy	10931	B F S F -	1	0	0	8.3	8.25	
22	9/21/15	C B	38	Optic atrophy	17146	B - S F ft -	1	0	0	8.3	8.15	7.75
23	10/ 7/15	M F	30	Chancere	11164	B F S F -	2	0	0	8.5	8.15	7.6
24	10/ 7/15	L D	28	Chancere	17970	B + S F -	0	0	0		8.25	
25	10/12/15	J L	30	Chancere	4185	B ft + S F -	0	0	0	7.95	7.9	7.65
26	10/12/15	P C	35	Retinitis	15779	B - S F -	3	0	0	8.1	8.05	
27	10/14/15	J L	30	Secondary syphilis	18124	B - S F -	0	0	0	8.35	8.15	7.7
28	10/14/15	M S	22	Chancere	18122	B - S F -	3	0	0	8.3	8.1	7.65
29	10/14/15	F C	13	Chancere	17834	B + + + S F -	76	+	+	8.3	8.1	7.65
30	10/23/15	L W		Mental symptoms	18555	B F S F -	2	0	0		8.25	
31	11/16/15	C W	39	Syphilis, syphilitic glau- tritis (?)	18820	B + + + S F -	1	0	0	8.3	8.25	
32	11/18/15	W	24	Chancere	18402	B F + S F -	0	0	0	8.3	8.15	7.5
33	10/19/15	O L	18	Secondary syphilis	17013	B + + + S F -	173	+	+	8.3	8.05	
Averages										8.26	8.11	7.61

\* B means blood S F means spinal fluid

results show, further, that in both groups the hydrogen ion concentration of the blood obtained from the same patient at the same time and similarly tested is in each instance greater than that of the spinal fluid, the average value for pH in the syphilitic cases being almost identical with that obtained in the normal cases

Nor was any marked alteration of the normal reaction observed in the spinal fluid obtained from patients with syphilitic affections of the central nervous system, such as tabes, general paresis and cerebrospinal syphilis. The average values for pH in this group, as recorded in Table 4, are slightly lower than the normal, but the differences are too small to be of real significance. A study of the reaction of the fluid in these cases brings up an interesting point, namely, the relationship between inflammatory conditions of the meninges and the reaction of the cerebrospinal fluid. Some authors<sup>15, 18</sup> entertain the view that in the presence of infection acid products are formed which render the cerebrospinal fluid acid. From the presence of a high cell count, that is, an average thirty-five cells with a maximum of 110 cells, in the spinal fluid of most of these patients, one may assume a chronic inflammatory condition to have existed, and yet no alteration in reaction was demonstrable. This, however, does not preclude the possibility that acute inflammatory conditions may be associated with a more acid reaction, that is, with an increase in the hydrogen ion concentration. So far as we are aware no positive proof has been brought forth to show that acid substances may form in acute inflammatory conditions of the meninges, and that these may produce an acidulation of the cerebrospinal fluid.

The possibility that the reaction of the fluid may be rendered more acid in cases of infection suggests a therapeutic problem of considerable importance. As has been shown by Crowe<sup>19</sup> hexamethylenamin is one of the few antiseptic drugs which can traverse the barrier of the choroid plexuses and pass from the blood stream into the cerebrospinal fluid. But in order to be effective in antagonizing infection, hexamethylenamin must, according to more recent studies,<sup>20</sup> be broken up into formaldehyde. This chemical change can occur only in an acid medium. Unless, therefore, it can be demonstrated that the spinal fluid becomes acidulated in the presence of infecting organisms and that hexamethylenamin is actually broken up into formaldehyde, considerable doubt must be entertained concerning the bactericidal power of this drug in combating infections of the meninges.

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18 Wingrave, W. Jour Laryngol, Rhinol and Otol, 1915, xxx, 270

19 Crowe, S. J. Bull Johns Hopkins Hosp, 1909, xx, 102

20 Burnam, C. F. THE ARCHIVES INT MED, 1912, x, 324. Hinman, F. Jour Am Med Assn, 1913, lxi, 1601

TABLE 4.—THE HYDROGEN ION CONCENTRATION OF THE CEREBROSPINAL FLUID IN SYPHILITIC AFFECTIONS OF THE NERVOUS SYSTEM INCLUDING TABES, GENERAL PARESIS AND CEREBROSPINAL SYPHILIS

Number of Case	Date	Name	Age	Diagnosis	Hospl tal Number	Wassermann*	Cell Count	Nonne	Noguchi	Reaction of Cerebrospinal Fluid, Value of pH	Reaction of Spinal Fluid, Value of pH	Reaction of Blood, Value of pH
34	8/24/15	H V	39	Tabes dorsalis	16893	B +++ S I ++	24	St +	+	8.3	8.15	
35	8/28/15	L K	46	Taboparesis	16953	B — S F —	1	0	0	8.3	8.25	
36	10/12/15	P A R	57	Tabes dorsalis	House 10923	B + S F —	0	0	0	8.1	8.0	
37	8/24/15	N L	37	Cerebrospinal syphilis	307	B +++ S F +++	12	—	—	7.95 7.95	7.75 7.75	
38	8/25/15	J J	50	Cerebrospinal syphilis	16944	B — S F ++	60	—	—	8.3	8.15	
39	8/26/15	J B	46	Cerebrospinal syphilis	16711	B +++ S F ?	110	—	—	8.25	8.15	
40	8/31/15	S T	52	Cerebrospinal syphilis	17037	B +++ S F —	2	0	0	8.2	8.1	7.7
41	10/ 7/15	D C	31	Myelitis luetica	14164	B — S F —	3	0	0	8.25	8.2	
42	10/ 7/15	H W	36	Cerebrospinal syphilis	11600	B — S I +++	15	0	0	8.15	8.15	7.75
43	10/12/15	G F	12	Cerebrospinal syphilis	17885	B ++ S F ?	57	—	—	7.95	7.75	7.65
44	10/10/15	W S	47	Cerebrospinal syphilis	18140	B +++ S F +++	51	—	—		9.1	
45	11/16/15	H Y	52	Cerebrospinal syphilis	18641	B — S I +	32	—	—	9.1	8.35	
46	12/ 8/15	O A	36	Cerebrospinal syphilis	19447	B + S I ++	28	—	—	8.4	8.15	7.75
47	12/18/15	S J	29	Cerebrospinal syphilis	19921	B + S F ?	28	0	0	8.3	7.95	7.60
Averages							35			8.22	8.08	7.69

\* B means blood, S F means spinal fluid

## SUMMARY

The colorimetric method of determining the hydrogen ion concentration of the cerebrospinal fluid gives constant and reliable results. For the reasons given, the method, when applied to cerebrospinal fluid, possesses greater accuracy than in the case of other biologic fluids, notably blood. The simplicity of the technic makes it applicable as a routine procedure in the examination of spinal fluids.

As determined colorimetrically, normal cerebrospinal fluid is more alkaline than blood, the difference in the hydrogen ion concentration of the dialysates of the two fluids being equal to 0.45, the value of pH for cerebrospinal fluid being 8.11, value of pH for blood, 7.66. No alteration from the normal reaction has been noted either in the blood or in the fluid of patients suffering from primary or secondary syphilis or from syphilitic affections of the nervous system. Thus far no study has been made of the reaction of the cerebrospinal fluid in acute inflammatory conditions of the meninges. The demonstration that a change in reaction does or does not occur would have an important bearing upon the value of hexamethylenamin as a therapeutic agent in the prophylaxis and treatment of meningeal infections.



# A METHOD FOR THE DETERMINATION OF THE ALKALI RESERVE OF THE BLOOD PLASMA \*

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Bicarbonates, alkali protein compounds and small quantities of alkali phosphates together constitute the alkali reserve of the blood plasma <sup>1</sup> Under normal conditions these substances are present in very constant quantities. A diminution in the alkali reserve is known as acidosis and may be recognized by a variety of clinical symptoms and by characteristic alterations in the composition of the blood, urine and alveolar air.

The alkali reserve maintains the plasma at a constant slightly alkaline reaction, despite the fact that acid products of metabolism are continually being poured into the blood. Chief among the acid products, so far as total quantity is concerned, is carbonic acid. Thus, as carbon dioxide enters the plasma circulating through the tissues and is taken up partly in combination and partly as dissolved carbonic acid. An almost infinitesimal change in reaction in the direction of acidity occurs. This slight change is sufficient to stimulate the respiratory center. The resultant pulmonary ventilation removes the excess of carbon dioxide and the plasma reaction returns to its original point. An excessive production of carbon dioxide in the tissues results in a greater change in the reaction of the plasma, with a consequent increased stimulation of the respiratory center and increased pulmonary ventilation. This tends to accomplish the removal of the extra carbonic acid. No depletion of the alkali reserve occurs.

If, however, a nonvolatile acid, such as sulphuric, phosphoric or beta-oxybutyric is poured into the plasma, a certain amount of the alkali reserve is neutralized and the reaction of the plasma shifts towards acidity. Increased pulmonary ventilation occurs, but this, of course, cannot effect removal of the nonvolatile acid. An extra amount of carbonic acid can be removed, however, so that less than the normal amount remains in the plasma. This decrease in carbonic acid may compensate for increase in nonvolatile acids and the reaction may return to the normal point. The alkali reserve, however, is depleted, as it is partially neutralized by the nonvolatile acid. When the plasma with its depleted alkali reserve again comes in contact with the tissues, the carbonic acid normally produced causes a greater change in reaction than

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\* Submitted for publication, April 17, 1916

\* From the Harriet Lane Home and the Department of Pediatrics, Johns Hopkins University

1 Plasma alone is here considered. The whole blood maintains its reaction in essentially the same way as the plasma alone.

when the alkali reserve was intact. As a result there is an overstimulation of the respiratory center, the evidences of which are hyperpnea and a diminished alveolar carbon dioxide tension. If the increased pulmonary ventilation is sufficient to maintain the carbonic acid content of the plasma at a low enough level, no appreciable change in reaction occurs. If, however, the alkali reserve is not replenished<sup>2</sup> and if acid continues to pour into the plasma, a time may come when the increased pulmonary ventilation can no longer compensate by removal of carbonic acid. In such an event, the reaction of the circulating plasma becomes constantly less alkaline until a point is reached which is incompatible with life. This point is, approximately, neutrality.

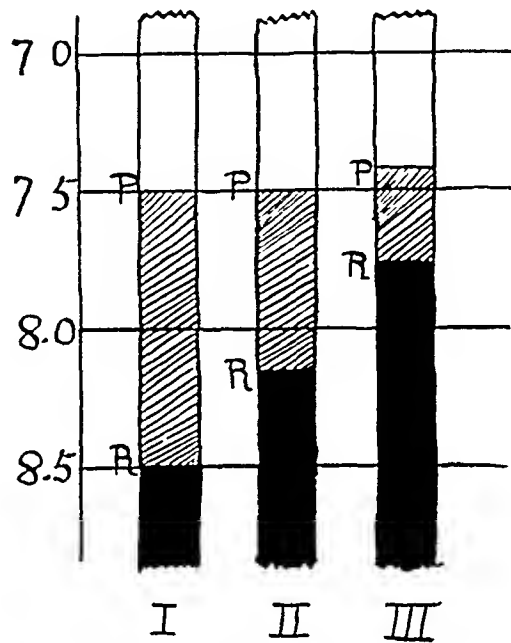


Fig 1—Showing relation between alkali reserve and reaction of the plasma *I*, plasma under normal conditions, *II*, plasma in mild acidosis, *III*, plasma in severe acidosis. Figures in left-hand column represent the negative logarithm of hydrogen ion concentration (pH). Black areas in the columns represent nonvolatile acid, and the shaded areas, carbonic acid.

The accompanying diagrams<sup>3</sup> illustrate the changes occurring in the plasma under the conditions described above.

The reaction of the plasma is expressed in terms of the negative logarithm of the hydrogen ion concentration (pH). According to this method of notation a reaction of 7.0 is the expression for neutrality. Figures less than this represent varying degrees of acidity, figures greater, corresponding degrees of alkalinity<sup>4</sup>. The figures given in the

<sup>2</sup> The alkali reserve may be replenished by administration of alkalis as such or as foods giving an alkaline ash. The body itself replenishes the reserve by production of ammonia and by the selective excretion of acid by the kidneys.

<sup>3</sup> Compare Barcroft. *Respiratory Function of the Blood*, Cambridge, 1914, Peabody. *Am Jour Med Sc*, 1916, cli, 184.

<sup>4</sup> For a more detailed explanation of this method of expressing reaction, see Levy, Rowntree and Marriott, *THE ARCHIVES INT MED*, 1915, xvi, 390.

diagram for reaction of the plasma are those obtained by the dialysis indicator method described below. They approximate the true values. In the columns (Fig. 1) the black areas represent nonvolatile acids, the shaded areas carbonic acid. Column *I* represents the plasma under normal conditions. The reaction (*P*), when measured under such circumstances that no carbonic acid is allowed to escape, is approximately 7.5. If the carbonic acid is entirely removed, the reaction becomes more alkaline and reaches the point 8.5, this final reaction (*R*) may be considered a measure of the effective alkali reserve. In the diagram the alkali reserve is represented by that part of the columns between the neutral point 7.0 and the points marked *R*. As the neutral point, at a given temperature, does not vary, the reaction at the point *R* is a quantitative expression for the alkali reserve.

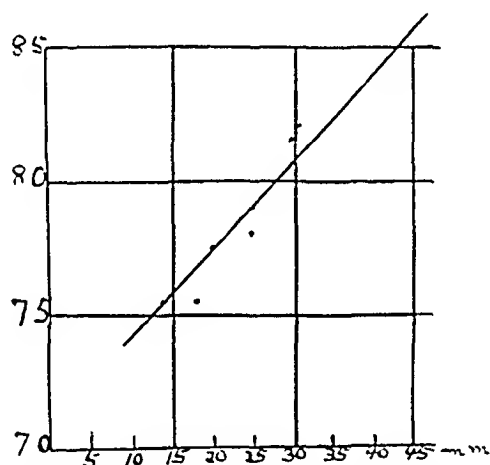


Fig. 2—Showing relation between alkali reserve of the plasma and alveolar air. Ordinates represent negative logarithm of hydrogen ion concentration of the dialysate from serum after removal of carbon dioxide (RpH), and abscissae, mm tension of carbon dioxide in alveolar air (Plesch-Higgins method).

Column *II* represents the condition of the plasma when a moderate degree of acidosis is present. The nonvolatile acids are increased, but carbonic acid is decreased, so that the actual reaction (*P*) remains practically the same as under normal conditions. The alkali reserve, however, is depleted so that when the carbonic acid is removed the reaction (*R*) differs appreciably from the normal.

5 This reaction varies with the alkali reserve, although, as a matter of fact, the two are not absolutely proportional. The lengths of the columns in the diagram are logarithmic and not actual. The shaded areas representing carbonic acid do not represent actual quantities present but the difference between the logarithms of the hydrogen ion concentration, before and after removing the amount of carbonic acid present. The difference is greater the greater the amount of carbonic acid, but the diagram is not to be interpreted as meaning that because the shaded area PR in Column *I* is twice as great as in Column *II*, that in *I* exactly twice as much carbonic acid is present.

Column *III* represents the condition of the plasma when the alkali reserve is so greatly depleted that the diminished amount of carbon dioxid can no longer compensate and an actual change in the reaction of the plasma, as it exists in the vessels, occurs. On removing carbon dioxid the reaction differs very greatly from the normal. The lengths of the shaded portions of the columns indicate, in a general way, the variations in tension of carbon dioxid in the plasma and hence in the alveolar air which is, presumably, in equilibrium with the plasma.

Provided the respiratory center does not vary in its excitability, the reaction of the circulating plasma is maintained at a constant point, except when a very marked acidosis, that is, depletion of the alkali reserve, occurs. The tension of carbon dioxid in the alveolar air generally bears a constant relation to the alkali reserve.

Since it is only in severe acidosis that changes occur in the reaction of the plasma, as it exists in the body, the measurement of the reaction, the hydrogen ion concentration, is a measure of the excitability of the respiratory center rather than of the degree of acidosis. This measurement may be most accurately made by the electrometric gas chain method, a somewhat difficult procedure and one not readily adaptable to clinical work. Recently an effort has been made to determine the reaction of the plasma by means of an indicator<sup>6</sup>

The method consisted in dialyzing serum or whole blood against salt solution in order to remove coloring matters and proteins. The hydrogen ion concentration of the dialysate was determined by means of the indicator, phenolsulphonephthalein, phosphate solutions of known hydrogen ion concentration being used as standards for comparison. At the outset of this work it was realized that the actual hydrogen ion concentration was not determined, the results, however, coincided closely with those obtained by the electrical method. In severe acidosis variations in the direction of acidity were encountered. The method seemed to indicate variations in the hydrogen ion concentration, although the variations observed were probably greater than those actually occurring. Serums from normal individuals showed a considerable range of variation, from 7.6 to 7.9, although duplicate determinations on the same sample almost invariably agreed. Since it is quite certain that in serum the reaction normally does not vary to any such extent as this, the variations observed must have been due to the fact that varying amounts of carbon dioxid were present. Carbon dioxid is lost if the blood is shaken in a tube, if it is left exposed to the air, or if it is obtained by cupping, the usual method of obtaining blood from infants. The carbon dioxid content may be greatly increased in blood drawn from an arm vein if the tourniquet

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<sup>6</sup> Levy, Rowntree and Marriott. *THE ARCHIVES INT. MED.*, 1915, xvi, 389

has been in place for some time previously, and especially if the forearm and hand have been exercised. I have observed values as low as 72 on the serum of normal individuals when obtained from an arm vein and values as high as 79 or 80 when the serum was obtained by cupping.

If the blood serum, after drawing, were placed in a Barcroft tonometer or some similar device and saturated with the subject's own alveolar air, more constant results might be obtained on normal individuals. In fact it is absolutely necessary to control the carbon dioxide content of the serum in some such way if results of any value are to be obtained. Even by thus increasing the accuracy of the method, its delicacy is not increased sufficiently to detect with certainty any but the severest grades of acidosis. If, however, the carbon dioxide is removed from the plasma as completely as possible by aeration, the unneutralized alkali reserve remains, and this may be measured by determination of the hydrogen ion concentration. As aeration of the plasma presents obvious technical difficulties, I have first allowed the serum to dialyze and have then aerated the dialysate and determined its reaction. To refer again to the diagrams, what is determined is the reaction R instead of P, as in the original method. Since P shows but slight variations in contrast with R, the latter measurement serves as a much more delicate method for detection and quantitative determination of acidosis. The principle of the method is the same as that previously described.<sup>6</sup> However, certain necessary changes in technic have been introduced.

**Apparatus Required.** Set of tubes containing standard phosphate mixtures, a solution of phenolsulphonephthalein in 0.8 per cent sodium chlorid, collodion sacks, pipet to measure 0.5 c.c., small test tubes for dialyzing and aerating, atomizer bulb, glass tube or pipet drawn out to a fine capillary point, color comparison box.

#### PREPARATION OF PHOSPHATE MIXTURES

*One-Fifteenth Molecular Acid Potassium Phosphate*—Of the pure, recrystallized salt ( $\text{KH}_2\text{PO}_4$ ), 9.078 gm. are dissolved in freshly distilled water. Two hundred c.c. of 0.01 per cent phenolsulphonephthalein are added and the whole made up to 1 liter with distilled water.

*One-Fifteenth Molecular Alkaline Sodium Phosphate*—The pure, recrystallized salt ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ) is exposed to the air for from ten days to two weeks, protected from dust. Ten molecules of water of crystallization are given off and a salt of the formula  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$  is obtained. Of this salt, 11.876 gm. are dissolved in distilled water. Two hundred c.c. of 0.01 per cent of phenolsulphonephthalein are added and the whole made up to 1 liter. The exact amount of indicator added is immaterial, provided the same amount of indicator

<sup>7</sup> Barcroft. *Respiratory Function of the Blood*, Cambridge, 1914.

is added to each of the phosphate solutions, and a corresponding amount is added to the salt solution, to be subsequently described. A small crystal of thymol is added to each solution to prevent the growth of molds. The solutions should be preserved in Jena or Non-sol glass vessels. The solutions are mixed in the proportions indicated below to obtain the desired pH.

TABLE 1—PROPORTIONS IN WHICH PHOSPHATE SOLUTIONS ARE MIXED

pH	7.0	7.2	7.4	7.6	7.8	8.0	8.2	8.4	8.6
Primary sodium phosphate, c c	37	27	19	13.2	8.8	5.6	3.2	2.0	1.0
Secondary sodium phosphate, c c	63	73	81	86.8	91.2	94.4	96.8	98.0	99.0

These solutions are placed in small test tubes, approximately 100 mm long by 8 mm internal diameter, of glass that does not readily give off alkali. The tubes are stoppered or sealed off. They should be kept in a dark place when not in use. Under these conditions, the solutions retain their colors for long periods of time.

#### PREPARATION OF SACKS

One ounce of celloidon, Anthony's negative cotton,<sup>8</sup> is dissolved in 500 c c of a mixture of equal parts of ether and 95 per cent alcohol. The solution is allowed to stand for a week in order to allow impurities to settle out. A small test tube with a flared mouth, 50 mm long by 6 mm internal diameter, is filled with the celloidon solution. This is slowly poured out as the tube is rotated in such a manner as to coat the sides evenly. The tube is clamped in the inverted position and allowed to drain for ten minutes, or until the odor of ether has disappeared.<sup>9</sup> The tube is then filled with cold water and a knife blade is run around the edge of the sack, to loosen it from the glass. Water is then run in between the sack and tube and the sack gently loosened and pulled out of the tube. It is preserved by complete immersion in water.

#### PREPARATION OF SALT SOLUTION

Eight gm of chemically pure sodium chlorid are dissolved in distilled water. Two hundred and twenty c c<sup>10</sup> of 0.01 per cent phenol-

8 Manufactured by the Ansco Company, Binghamton, N. Y. This contains 30 per cent of water and must be rinsed once or twice with alcohol before being dissolved.

9 Sacks that have been dried too long become very brittle and impermeable. If not dried a sufficient length of time, the sack becomes white and cloudy on the addition of water.

10 The concentration of indicator in the salt solution is purposely made 10 per cent greater than in the phosphate mixtures, as during the dialysis a certain amount of indicator is lost by passing into the sack.

sulphonephthalein solution are added and the whole made up to one liter with distilled water. The solution should contain no free alkali and no acid other than carbonic. The solution is tested by boiling a little of it for a minute or so in a Jena glass test tube, in order to expel carbonic acid<sup>11</sup>. The solution is quickly cooled under the tap and compared with the phosphate standards. Its reaction should be 7.0. If the reaction differs from this it may be corrected by the addition of a few drops of very dilute acid or alkali to the whole solution. The salt solution must be kept in a vessel of Jena or Non-sol glass, or in a vessel of ordinary glass that has been well paraffined on the inside.

#### METHOD OF DETERMINATION

The determination must be carried out in a room free from acid or ammonia fumes. Either serum, oxalated plasma or blood may be used. Serum is to be preferred, as the addition of oxalate, unless exactly neutral, introduces a source of error. The blood should be collected in a small tube and the serum separated as quickly as possible, preferably by centrifuging<sup>12</sup>. Hemolysis must be avoided.

Exactly 0.5 c.c. of serum is pipetted into one of the small collodion sacks, which has previously been washed inside and out with the salt solution<sup>1</sup>. The sack is lowered into a small test tube, approximately 8 mm internal diameter and 50 mm long, containing 2 c.c. of the indicator salt solution. The level of the fluid on the outside of the sack should be at least as high as that on the inside. At the end of seven minutes the sack is removed and the dialysate transferred to a clean test tube 100 to 140 mm long and having the same diameter as the tubes containing the phosphate standards. A rapid current of air is bubbled through the solution in order to remove carbon dioxide. This is accomplished by means of an atomizer bulb connected with a narrow glass tube drawn out to a capillary point. The air current should be as rapid as possible without blowing liquid out of the test tube<sup>14</sup>. Blow-

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11 If boiled in a soft glass tube, alkali is given off from the glass and the solution is colored pink. Instead of boiling to remove carbon dioxide, the solution may be aerated with a current of air that has been freed from carbon dioxide by passing through a strong solution of sodium hydroxide.

12 If carbon dioxide escapes from the plasma as a result of shaking or allowing the blood to remain exposed to the air, a passage of alkali from the plasma into the cells occurs with a resultant slight diminution in the alkali reserve of the plasma. Once the plasma or serum is separated from the corpuscles, loss of carbon dioxide is without effect on the alkali reserve.

13 In washing the sack, no part but the top edge should be touched with the fingers. The sack is emptied by tipping it with a clean, glass rod or with a microscopic slide. Sacks may be used more than once, providing they are thoroughly washed with salt solution after each test.

14 Foaming rarely occurs. It may be present as a result of allowing some serum to spill over the outside of the sack. In case foaming is great enough to be troublesome, it may be prevented by adding a drop of octyl alcohol or toluol.

ing is continued for three minutes and then the color in the tube is compared with that in the standard phosphate tubes, interpolating when necessary<sup>15</sup> The reading is a measure of the reserve alkalinity, it is the value  $R$  referred to in Figure 1 For convenience of expression we shall refer to this value as the "RpH" of the serum, to differentiate it from the "pH" as determined in the method previously described by Levy, Rowntree and Marriott

#### RESULTS OBTAINED

**Normal Individuals** The serums of a large number of normal adults were examined by the method described In every instance the RpH was found to be  $8.5 \pm 0.05$ , provided the subjects examined were on a general mixed diet A normal adult's serum drawn after a fast of sixteen hours gave a reading of 8.35 The serums of infants gave values slightly lower than those of adults For normal infants under one year of age, a value of 8.3 for the RpH of the serum was not infrequently encountered This may be due partly to the fact that infant's blood is usually obtained by cupping, the lower value, however, is more likely an evidence of the tendency towards acidosis that is known to be present in infants

This accords well with the observed fact that the carbon dioxide tension in the alveolar air of infants<sup>16</sup> is lower than that of adults, and that the combined carbon dioxide of the plasma is less<sup>17</sup> in infants and that the ammonia coefficient in the urine is often higher This slight acidosis might well be the result of the more active metabolism of infants, leading to a proportionately greater production of acids

#### ACIDOSIS

A series of cases exhibiting clinical or laboratory evidences of acidosis has been studied The cases included nephritis and diabetes in adults, and nephritis, recurrent and idiopathic acetoneuria, and severe diarrheas in children The diarrheal cases were of the type described by Howland and Marriott<sup>16</sup>

The results in the column headed RpH, Table 2, represent the hydrogen ion concentration of the dialysate after removal of carbon dioxide The results in the column headed pH are those obtained

<sup>15</sup> The comparison is conveniently made with a box similar to that used with the Sahli hemoglobinometer, but containing places for three instead of two tubes It is a small flat box of blackened metal 55 by 45 by 20 mm, backed with opal glass and with three slits open on the front Readings should be made at temperatures between 20 and 25 C If the room temperature is higher or lower than those limits, the colorimeter with tubes should be immersed in water at 20 to 25 C

<sup>16</sup> Howland and Marriott *Am Jour Dis Child*, 1916, xi, 309, Marriott *Jour Am Med Assn*, 1916, lxxvi, 1594

<sup>17</sup> Van Slyke Unpublished results



TABLE 2—DEGREE OF ACIDOSIS IN TWENTY-FIVE CASES BY THE MODIFICATION OF THE INDICATOR DIALYSIS METHOD FOR DETERMINATION OF THE ALKALI RESERVE (RpH)

Case No	Date	Age, yrs	pH	RpH	Alveolar CO <sub>2</sub> Tension	
1*	7/21/15	45	7.6	8.2	36	Diabetes Carbohydrate free diet Ammonia coefficient in urine 11.7 per cent Acetone bodies in blood, 67 mg per 100 gm
2*	4/ 7/16	43	7.5	8.0	28	Diabetes Low caloric diet Ammonia coefficient in urine 20 per cent Acetone bodies in blood 57 mg per 100 gm
3*	1/19/16	21	7.3	7.8	21	Chronic diffuse nephritis Uremia Hyperpnea Drowsiness Blood nonprotein N 189 mg
3	1/28/16		7.7	8.5		Alkali administered Patient had daily doses of 40 gm sodium bicarbonate after Jan 19, 1916 Hyperpnea no longer present Plasma CO <sub>2</sub> , 66 vols per cent
4§	2/10/16	13	7.35	8.2	32	Congenital polycystic kidney Patient in fair condition Some nocturnal dyspnea
4	2/19/16		7.35	7.8	25	Patient very dyspneic Vomiting Plasma CO <sub>2</sub> , 21 vols per cent
4	3/ 3/16		7.7	8.4	38	Alkali administered daily since Feb 19, 1916 Patient in good condition No dyspnea
5†	3/ 1/16	41	7.2	7.35	11	Pyonephrosis, double Coma Marked hyperpnea Phenolsulphonaphthalein 1½ hours, 0 Blood urea nitrogen, 193 mg Plasma CO <sub>2</sub> , 14.7 vols per cent
5	3/ 2/16		7.55	7.9		Alkali administered Intravenous injection of 400 cc of 4 per cent solution sodium carbonate six hours previously Same dose ten hours previously Patient in coma
6*	3/14/16	23	7.4	8.0		Chronic diffuse nephritis Secondary anemia Blood nonprotein nitrogen, 212 mg Plasma CO <sub>2</sub> , 40 vols per cent
7†	3/14/16	36	7.0	7.3		Chronic nephritis Lead poisoning Arteriosclerosis Uremia Hyperpnea Sellards' test, colorless on evaporation Plasma CO <sub>2</sub> , 11 vols per cent
7	3/15/16		7.6	7.9		Alkali administered Twelve hours previously, patient received 500 cc of sodium bicarbonate intravenously No deep breathing Sellards' test, pink on evaporation Total nonprotein nitrogen, 200 mg Plasma CO <sub>2</sub> , 28 vols per cent
7	3/21/16		7.6	7.95		Alkali administered Patient given 4 gm of sodium bicarbonate by mouth every four hours since March 15, 1916 Sellards' test, pink color Plasma CO <sub>2</sub> , 34 vols per cent
3†	3/15/16	54	7.45	7.8		Arteriosclerosis of renal vessels Uremia, Hyperpnea Coma Sellards' test, colorless Plasma CO <sub>2</sub> , 19 vols per cent Phenolsulphonaphthalein, 3 per cent in two hours
9†	3/15/16	50	7.6	7.9		Chronic diffuse nephritis Uremia Drowsiness Sellards' test, pink on evaporation Phenolsulphonaphthalein, 2½ hours, 0 Hyperpnea Plasma CO <sub>2</sub> , 34 vols per cent
10*	3/17/16	39	7.6	7.9		Secondarily contracted kidney Uremia, Hyperpnea
11†	4/ 6/16	39	7.35	7.9		Acute and chronic nephritis Hyperpnea Edema
12	6/27/15	6	7.2	7.9		Idiopathic acetoneuria Marked hyperpnea Acetone bodies in blood, 26 mg

TABLE 2—DEGREE OF ACIDOSIS IN TWENTY-FIVE CASES BY THE MODIFICATION OF THE INDICATOR DIALYSIS METHOD FOR DETERMINATION OF THE ALKALI RESERVE (RpH)—(Continued)

Case No	Date	Age, Yrs	pH	RpH	Alveolar CO <sub>2</sub> Tension	
12	6/28/15		7.9	8.4		Alkali administration Twenty gm sodium bicarbonate by mouth, 6 gm by rectum Patient in good condition, breathing normally
13	1/ 9/16	2	7.2	7.75	20	Recurrent acetoneuria Coma Marked hyperpnea Acetone bodies in blood, 136 mg
13	1/ 9/16		7.7	8.3		Alkali administered Four and a half gm sodium bicarbonate given intravenously three hours previously
13	1/10/16		7.5	8.1		Alkali administered Patient received 4 gm sodium bicarbonate by mouth in past 24 hours Recurrence of coma with hyperpnea
14	1/14/16	3	7.5	8.2		Recurrent acetoneuria Vomiting, drowsiness Acetone bodies in blood, 84 mg
15	2/ 8/16	3	7.4	7.9	20	Idiopathic acetoneuria Hyperpnea Drowsiness Acetone bodies in the blood, 83 mg
16	2/26/16	10 mo	7.4	7.9	24	Diarrhea Vomiting Acetoneuria Hyperpnea Acetone bodies in blood, 69 mg Plasma CO <sub>2</sub> , 37 vols per cent
16	2/26/16		7.9	8.6		Alkali administered Two hundred cc 2 per cent sodium bicarbonate subcutaneously followed by 2 gm sodium bicarbonate by mouth every two hours for ten hours preceding
17	6/15/15	1	7.65	8.15		Ileocolitis Acetoneuria
18	6/ 6/15	7 mo	7.75	8.15	30	Diarrhea Acetone bodies in blood, 35 mg
19	7/13/15	6 mo	7.3	7.9	25	Severe diarrhea Hyperpnea Sellards' test colorless on evaporation Acetone bodies in blood, 21 mg
20	7/29/15	1	7.3	7.6		Severe diarrhea Hyperpnea
21	7/31/15	1	7.5	8.15	34	Diarrhea Acetone bodies in the blood, 23 mg
22	8/ 5/15	3 mo	7.2	7.55	14	Diarrhea Hyperpnea Acetone bodies in blood, 19 mg Hb dissociation curve (Barcroft), 17.8 per cent saturation at 17 mm
23	7/20/15	7 mo	7.25	7.45		Diarrhea Marked hyperpnea Acetone bodies in blood, 22 mg Hb dissociation curve (Barcroft), 13 per cent saturation at 17 mm
24	3/17/16	2	7.5	7.9	24	Diarrhea Hyperpnea
25	4/ 6/16	2 mo	7.05	7.55	18	Diarrhea Hyperpnea Acetone bodies in the blood, 24.7 mg

\* I am indebted to Drs T O Janeway and H O Mosenthal for permission to study these cases occurring in their service at the Johns Hopkins Hospital

† I am indebted to Drs T R Boggs and T P Sprunt for permission to study these cases occurring in their service at the City Hospital

‡ I am indebted to Dr N M Keith for permission to study this case occurring in his service at the Brady Urological Institute

§ I am indebted to Dr L F Barker for permission to study this case, which occurred in his service at the Johns Hopkins Hospital

according to the method of Levy, Rowntree and Marriott, as originally described and without removal of carbon dioxide

In all the cases of acidosis studied the R<sub>p</sub>H of the serum showed deviations from the normal. The more severe the acidosis, as indicated clinically or by various laboratory methods, the lower were the figures obtained for the R<sub>p</sub>H. Especially striking was the parallelism between alveolar carbon dioxide tension and the R<sub>p</sub>H. The accompanying curve illustrates graphically the relation<sup>18</sup>. The two values should correspond, as explained above, provided the respiratory center does not vary in its excitability and the pulmonary epithelium is not damaged in such a way as to prevent equilibrium being attained between the air in the pulmonary alveoli and the blood in the pulmonary capillaries. Thus a hyperexcitable respiratory center should lead to a low alveolar carbon dioxide tension, with a coincident normal alkali reserve. A diminished permeability of the pulmonary epithelium would result in a lowering of carbon dioxide tension in the alveolar air, but not necessarily to a diminution in the alkali reserve of the plasma.

In a number of instances the combined carbon dioxide of the plasma was determined according to the method described by Van Slyke<sup>19</sup>. The results obtained were in a general way proportional to the R<sub>p</sub>H of the serum. The effect of alkali therapy in replenishing the alkali reserve is shown in the results obtained on cases 3, 4, 5, 7, 12, 13 and 16. The R<sub>p</sub>H invariably shows an increase following administration of alkalis, but does not necessarily reach its normal value. It is in connection with the alkali therapy that we have found the method of especial value, as it gives information as to the probable amount of alkali needed to replenish the reserve. A determination following the administration of alkali shows whether the amount has been sufficient.

#### INTERPRETATION OF RESULTS

The values obtained for the R<sub>p</sub>H of the serum may, in the light of our experience, be interpreted as follows:

Values for the R<sub>p</sub>H of from 8.4 to 8.55 correspond to alveolar carbon dioxide tensions of from 38 to 45 mm., and are to be considered as normal values for adults. Values between 8.0 and 8.3 correspond to alveolar carbon dioxide tensions of from 28 to 35 mm. and indicate a moderate degree of acidosis.

When the value for R<sub>p</sub>H is as low as 7.7, corresponding to an alveolar carbon dioxide tension of 20 mm., the individual is in imminent danger. During coma, an R<sub>p</sub>H as low as 7.3 corresponding to an

18 Alveolar air was collected by the Plesch-Higgins method and analyzed either by means of the Haldane apparatus or by the colorimetric method (Marriott Jour Am Med Assn, 1916, lvi, 1594)

19 Van Slyke Proc Soc Exper Biol and Med, 1915, xi, 165

alveolar air of 11 mm, has been observed. In infants under 1 year of age a value for  $RpH$  of 8.3, corresponding to 35 mm tension in the alveolar air, is not to be considered abnormal.

It has been our experience in general, in this clinic, that unless the  $RpH$  of the serum is below 7.9, the acidosis may be successfully combated by dietetic regulation or by the administration of alkali by mouth. When the  $RpH$  of the serum falls below 7.9, intravenous administration of alkali is usually indicated.

#### SUMMARY

Acidosis implies a diminution of the alkali reserve of the blood plasma, though not necessarily a change in its hydrogen ion concentration.

A simple and rapid method for the measurement of the alkali reserve is described. It is a modification of the indicator dialysis method for the determination of hydrogen ion concentration, but is more accurate and gives more information than that method.<sup>20</sup>

The method serves for the detection and accurate quantitative estimation of the degree of acidosis.

The results obtained on twenty-five cases of acidosis are reported.

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<sup>20</sup> Standardized phosphate mixtures sealed in tubes, the color comparison box, tubes and accessories used in the method may be obtained from Hynson, Westcott & Company, Baltimore.

## BOOK REVIEWS

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DISEASES OF THE DIGESTIVE ORGANS WITH SPECIAL REFERENCE TO THEIR DIAGNOSIS AND TREATMENT By CHARLES D. AARON, Sc D, M D, Professor of Gastro-Enterology in the Detroit College of Medicine and Surgery Cloth Price, \$6 net Pp 790, with 202 illustrations Philadelphia Lea and Febiger, 1915

In contrast with Professor Mendel's book, which contains an extraordinary amount of things new and true in small compass, Dr Aaron's book succeeds in spreading out a mass of misinformation over 750 large pages, in one of the most unsatisfactory books that has come to the reviewer's attention for a long time. In the first place, its utterly uncritical laboratory methods and methods of diagnosis are shoveled in wholesale, without any choice between the valuable and valueless. On its clinical side it is equally unsatisfactory. The account of gastric ulcer, for example, contains within the first five lines the following statements: "The symptoms of gastric ulcer are at first ill defined, resembling those of gastritis. The discomfort is soon followed by nausea and regurgitation or vomiting. A boring pain is characteristic of gastric and duodenal ulcer, it always comes on within an hour after eating." According to the reviewer's experience, not one of these symptoms is even approximately true. The author goes on to say that it is strictly necessary to prohibit the patient from all manipulations of the epigastric region, as well as from all pressure produced by dress or work. It is hard to imagine anything whereby useless apprehension and worry could be more easily produced in the patient than by this statement. He recites a number of meats, "permissible for gastric patients." These are beef, veal, lean pork, hare, deer, fowl, squab, partridge, pheasant. Apparently, lamb is fatal, since it is nowhere mentioned.

Under his therapeutics he states that in cases of acute intestinal or gastro-intestinal catarrh, opium in some form is always indicated. In discussing nervous eructations he says: "The air which is belched up has gained entrance to the stomach by some means, though it is rare that atmospheric air is directly aspirated by the stomach." To anyone who has watched with the fluoroscope while the air sucked into the stomach comes rushing down the esophagus and then is expelled again, this statement must be surprising.

Four pages are devoted to gastralgia, described as a condition peculiar to individuals of nervous temperament. Although he says that diagnosis is made by excluding organic diseases of the stomach and intestines and the more remote viscera, he also says in the same paragraph that among the recognized causes of gastralgia are syphilis, gallstones and chronic appendicitis. The meaning of the last statement cancels that of the first.

Rectal feeding is cordially recommended, and among the foods mentioned as valuable for this purpose are eggs, meat, butter and wheat flour. He seems totally oblivious of the fact that modern investigations have shown that little or no absorption of any of these foods occurs in the rectum.

Among the predisposing causes of gastric ulcer he mentions achylia gastrica. Scirrhus carcinoma, he says, is made up of an abundance of connective tissue.

In his account of liver abscess he says: "The facial expression is one of suffering. The eyes are sunken and the conjunctivae have a mother-of-pearl-like luster. The high position of the diaphragm often gives rise to dyspnea." No considerable clinical experience would have taught him that none of these things is true in the majority of cases of liver abscess.

Under discussion of tapeworms he says that nasal and anal pruritus is common in cases of infection with most tapeworms, but rarely seen with *Hymenolepis nana*. Here we seem to have reminiscence of the old wives' legend that a child who scratches his nose has worms.

Under the account of trichiniasis there is no mention of eosinophilia as a diagnostic sign. The difficulties and dangers of esophagoscopy are not in any way hinted at. In fact he says the procedure involves practically no danger.

As far as the present reviewer can see, one would have no need to be a doctor to write such a book. Clinical experience is hardly visible anywhere. Any one who knew the works of Ewald, Boas or Einhorn could have written the book. The multiplicity of such treatises is one of the worst signs of modern medicine.

CHANGES IN THE FOOD SUPPLY AND THEIR RELATION TO NUTRITION. By LAFAYETTE B. MENDEL, Professor of Physiologic Chemistry in the Sheffield Scientific School of Yale University. Cloth. Price, 50 cents. Pp 61. New Haven. Yale University Press, 1916.

Yale University Press is to be congratulated upon two remarkable little books each containing multum in parvo—Prof. Graham Lusk's, "The Fundamental Basis of Nutrition," and the little book now under review, Prof. L. B. Mendel's "Changes in the Food Supply and Their Relation to Nutrition."

Professor Mendel starts with Sir William Crookes' forecast made in 1898, to the effect that by 1931 we should have reached the limit of wheat production upon the earth, while the population would presumably be still increasing, and this Sir William regarded as a most ominous prediction, as he regarded wheat as "the most sustaining food grain of the great Caucasian race." Professor Mendel agrees that this estimation as to wheat acreage is probably correct, but that in the first place the yield by acre would be increased and that, moreover, any alarm in relation to wheat acreage fails to take into consideration the altered prospects arising out of modern increase of knowledge of the science of nutrition. Wheat shortage does not mean food shortage, for new grains are coming in. One of these is the proso millet, another, grain sorghum, or kaoliang, both long known as constituents of the diet of mankind and especially valuable because they are drought-resistant and will grow where the staple small grains requiring moisture fail. Both of them have been tested, in a semi-public way, as foods, by Hansen of the South Dakota Agricultural Experiment Station. Cotton seed flour is also clamoring for recognition. Professor Mendel points out, further, that cold storage, in its recent developments, has a most important bearing on the food supply. Fresh fish, when frozen, can be preserved without undergoing any important change for at least two years. Desiccated milk preserves all its nutritive features so that several investigators, including Professor Mendel himself, have raised small animals into a second generation, with dried milk as the chief component of their ration. He points out also the use of waste products, such as cotton seed oil, oleo oils from beef, slaughter house blood, corn syrups and old butter successfully renovated. It is conceivable also that cellulose might be converted into available carbohydrate by chemical procedures.

Increasing use of nuts, as in popular peanut butter, figures as one of the so-called substitutes for meat, though, as he points out, it could be more truly said from an evolution point of view, that meat is a substitute for nuts.

Another important section of the book deals with changes of fashion in diet. Because the more well-to-do classes have for some time been in the habit of eating a great deal of meat, dietary fashions are imitated by others, not because they need the meat, but because it is a matter of pride for them to follow as best they can the more well-to-do classes in their diet.

The use of fresh fruits, he says, has been enormously extended in the last twenty years in the temperate zones. Since 1840 the value of the orchard products in the United States increased from \$8,000,000 to \$140,000,000. Both with fruits and with cereals, advertising is now successful in changing our habits away from the excessive use of meat. Breakfast foods and bakers'

bread are being produced upon a scale never equaled before. Bread-making is becoming a factory problem. The use of butter, cheese, nuts, candy, green vegetables, such as peas and asparagus, is now increasing.

All of these changes are in the right direction and against the senseless imitation of the plutocratic diet. The grape juice industry has grown by leaps and bounds, so that Secretary Daniels' grape juice is inevitable to become one of the national drinks.

Professor Mendel suggests that the enormous percentage of waste in the apple crop (nearly 25 per cent) may be transformed by new methods into apple syrup and fresh cider.

Another influence making against the excessive meat diet is the dairy lunch room innovation. The dairy lunch room is not as cheap as the old home dinner pail and lunch basket, but contains a larger proportion of cereal in a more inviting form.

The present European war, he thinks, will tend in the same direction. The regimen of South German households is being gradually substituted for the excessive meat diet of the northern provinces. Variety of food and the use of fish, rather than artificially preserved foods, are still of great importance because of the danger that we shall lose the accessory diet factors or vitamins in the processes of preservation or manufacture.

I have been able to suggest only some of the most important features of this most interesting book, which should be read from cover to cover by all who are concerned with the problem of nutrition.

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## CLINICAL CALORIMETRY

### NINTH PAPER

#### FURTHER MEASUREMENTS OF THE SURFACE AREA OF ADULTS AND CHILDREN\*

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In paper 5<sup>1</sup> of this series a method was described by means of which it was possible to determine the surface area of living subjects. On the basis of the measurements of five persons of widely varying body shapes, a formula was devised by Mr. Delafield Du Bois which gave an average error of only 1.7 per cent when applied to the persons measured. The number of subjects was rather small and it has seemed best to continue the work and apply the formula to persons of unusual shapes.

Since the publication of the previous paper, in which the literature was reviewed, a number of references have come to light largely through the attention of Dr. Francis G. Benedict of the Nutrition Laboratory of Boston. The work of Sicheff<sup>2</sup> is of considerable importance. Working in Gundobin's clinic he applied the methods used by Meeh to twenty-four children from the ages of 1 day to 15 years, and to one adult. He found the surface area proportional to the two third power of the weight, but the average constant by which this should be multiplied is 107, according to his figures, instead of Meeh's figure of 119. In the case of the adult the constant would be 88, which is at such variance with the results of other investigators that it would seem as if some error must have crept into the calculations in this one case.

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\* Submitted for publication Feb. 4, 1916.

\* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital.

1 Paper 5, Clinical Calorimetry, THE ARCHIVES INT. MED., 1915, xv, 868.

2 Sicheff (Ssytscheff), A. I.: Measurement of the Volume and the Surface of the Body of Children According to Age, Inaug. Dissert., Petrograd, 1902. The tables are given in Gundobin, Die Besonderheiten des Kindesalters, Berlin, 1912. We are indebted to Dr. Benedict for permission to consult the translation of the original article in the Nutrition Laboratory.



Variot and Saint Albin<sup>3</sup> have measured the surface of a number of children using pieces of tin foil, and Maurel<sup>4</sup> has worked out the relationship of the thorax dimension to surface area. Letulle and Pompilian<sup>5</sup> in 1906 used a method of determining surface area somewhat similar to the formula adopted by D. Du Bois nine years later. They consider that the surface of the body consists of a number of trapezoids, one covering the upper arm, one the forearm, one the hand, one for each finger, etc. They calculate the area of each trapezoid from the length of the part and the circumference at the two borders which form the sides of the figure. The errors inherent in this method become evident when one looks at the factors used in the "Linear Formula" of D. Du Bois. It is necessary to correct the average length and breadth of each part by a factor to obtain the true surface. Lassabliere<sup>6</sup> measured the surface of a large number of children by marking out the skin in geometrical patterns and determining the area by means of a perimeter. He found the skin area proportional to  $10.5 \text{ Wt}^2$  or to  $0.92 \text{ Ht}^2$  or to  $2.3 \text{ Perim}^2$ , Wt being the kilograms of body weight, Ht the height in centimeters and Perim the circumference of the thorax at the level of the nipples.

#### INDIVIDUALS MEASURED

Anna M.—This was the cadaver of a child 21 months old, weighed and measured about two hours after death. The subject was small for her age and had suffered from rachitis, the epiphyses at the wrists were large and the thorax was pigeon-breasted, being narrow and very deep anteroposteriorly. The child had pertussis and developed a fatal pneumonia.

Fabian R. S., aged 12 years, 10 months, an unusually well formed boy with no signs of puberty as yet. He was muscular and rather short for his age. He served as the subject for one of the calorimeter experiments described in Paper 12.

Gerald S. 18 years old, tall and much emaciated. He was a diabetes patient and a complete description of his case is to be found in Paper 17. He was given the Allen fasting treatment from November 11 to 19 and the measurements were taken December 1 after he had been on a maintenance diet for about a week. His weight at one time dropped to 38.7 kg, but increased to 45.25 kg as a result of food ingestion, and also on account of an invisible edema.

#### ERROR IN PREVIOUS PAPER

A brief preliminary note about the measurements of Gerald S. was given at the end of Paper 5<sup>1</sup> of this series. The discrepancy between the calculated

3 Variot and Saint Albin. La mensuration de l'aire cutanee des jeunes enfants par l'enveloppement avec des feuilles d'etain, Bull. Soc. de pediat. de Paris, 1903, v, 307.

4 Maurel, E. Adaption de la section thoracique a la surface cutanee par rapport au poids, depuis la naissance jusqu'a l'age adulte, Compt. rend. Soc. de biol., 1904, lvi, 980.

5 Letulle and Pompilian. Methode de recherche applicable a l'etude de la nutrition, Rev. Soc. scient. d'hyg. aliment., 1906, iii, 708.

6 Lassabliere, P. Evaluation de la surface cutanee chez le jeune enfant, Compt. rend. Soc. de biol., 1910, 339.

TABLE 1—MEASUREMENTS USED IN FORMULA

	Anna M., Cm	Fabian S., Cm	Gerald S., Cm	Emma W., May 3, Cm	Emma W., May 13 and 17, Cm	R H S June 18, Cm	Robert L., Cm	Harry J., Right Side, Cm	Harry J., Left Side, Cm
A—Around vertex and chin	19 1	61 5	62 2	61 1		67 0	67 9	64 6	
B—Around occiput and forehead	41 0	51 1	51 2	55 0		58 0	57 2	55 5	
F—Acromion to lower border of radius	22 9	49 5	65 5	58 6		67 7	51 6	59 1	57 7
G—Circumference of arm at upper border of axilla	10 5	20 5	20 0	27 5	27 0	26 3	33 6	32 2	34 5
H—Largest circumference of forearm	11 9	19 7	21 0	23 4	23 8	25 1	26 2	23 2	29 0
I—Smallest circumference of forearm	9 1	13 3	15 0	11 3	14 8	16 7	16 1	16 2	16 5
J—Lower posterior border of radius to tip of second finger	8 7	16 4	19 8	17 5		21 9	19 2	17 9	
K—Circumference of hand at knuckles	8 6	17 1	19 9	17 6		20 6	20 6	20 2	
L—Suprasternal notch to upper border of pubes	26 0	46 0	51 3	51 3		53 6	56 7	50 0	
M—Circumference of abdomen at umbilicus	35 1	56 8	61 7	71 2	70 1	69 8	92 6	78 2	
N—Circumference of thorax at nipples in male and just above breasts in female	38 6	66 2	78 5	81 0	83 0	85 9	100 6	96 2	
O—Superior border of great trochanter to lower border of patella	16 0	37 8	44 7	45 7		50 3	47 5		
W—Superior border of pubes to lower border of patella	14 4	33 7	44 9	41 7		46 3			
P—Circumference of thigh at perineum	20 6	41 2	41 1	53 7	55 3	48 3	52 7		
Q—Circumference of hips and buttocks at level of trochanters	39 5	69 7	76 5	93 8	93 2	87 0	91 9		
R—Sole of foot to lower border of patella	16 0	36 1	48 3	45 3		53 1			
S—Circumference at lower border of patella	14 2	27 6	31 7	32 0	34 8	31 8			
T—Length of foot, including great toe	10 5	21 4	26 0	23 3		27 5			
U—Circumference at base of little toe	8 9	19 8	21 2	21 3		21 7			
V—Smallest circumference of ankle	9 9	16 5	17 8	20 3		23 8			

and measured areas of the thorax was so much greater than in any other case that an error was suspected. It became apparent that the recorded length of the thorax was 10 cm too short. This measurement L had been determined by subtracting the distance from foot to upper border of the pubes from III, the distance from foot to suprasternal notch. The recorded measurements in the case of Gerald S from the sole of the foot were as follows: "To suprasternal notch, 134.5 cm", to outer end of clavicle, 145.8, to upper border of axilla, 136.2, to tip of ensiform, 125.0, to the nipples, 134.3, height, 171.8. It was evident that the suprasternal notch must have been more than 0.2 cm above the nipples. To find its correct position the measurements of the five subjects whose shape was nearest to that of Gerald S were tabulated and the average percentage of the height shared by the distance between suprasternal

TABLE 2—MEASUREMENTS NOT USED IN FORMULA

	Anna M	Tablan S	Gerald S	Emma W May 3	R H S June 18
I—Weight, kg	62.7 Cm	32.74 Cm	45.25 Cm	57.62 Cm	63.00 Cm
II—Height or length	73.2	141.5	171.8	164.8	184.2
III—Sole of foot to suprasternal notch	54.8	114.7	144.5	135.7	152.2
IV—Sole of foot to nipples	50.4	107.0	134.3	123.9	140.2
V—Sole of foot to upper border of axilla	53.2	109.8	136.2	127.9	145.8
VI—Sole of foot to tip of ensiform	45.6	100.2	125.0	117.5	129.8
VII—Sole of foot to superior border of great trochanter	30.2	73.7	93.0	88.5	103.1
VIII—Sole of foot to perineum	26.6	64.2	86.0	76.4	92.1
IX—Circumference of thorax at tip of ensiform	41.2	65.0	76.5	74.0	78.8
X—Tip of second finger to upper border of axilla	—	—	67.5	—	—
XI—Tip of second finger to tip of olecranon	18.6	37.9	46.9	43.3	51.9
XII—Tip of second finger to metacarpophalangeal joint	4.9	9.8	10.8	10.1	12.3
XIII—Tip of olecranon to lower border of radius	9.8	22.3	28.0	26.0	31.5
XIV—Tip of olecranon to acromion process	13.0	28.0	37.5	32.8	37.7
XV—Circumference of arm at insertion of deltoid	10.4	19.4	18.7	26.0	25.6
XVI—Circumference of arm at belly of biceps	10.6	19.1	18.3	23.8	25.1
XVII—Circumference of thigh half way between anterior superior spine of ilium and lower border of patella	17.8	39.2	37.6	52.2	47.0
XVIII—Largest circumference of calf	13.0	26.6	27.2	35.0	31.0
XIX—Circumference of foot at heel	11.9	26.5	30.2	29.7	31.5
XX—From back of neck around superior maxilla	31.8	42.5	43.5	45.0	48.3
XXI—Around neck just below larynx	17.5	29.0	30.8	33.5	36.5
XXII—Around shoulders at level of heads of humeri	39.8	73.5	87.4	91.0	103.6

notch and various neighboring parts was calculated. The projected location of the suprasternal notch in Gerald's case according to three different methods was 145.6, 142.4 and 144.2. The measurement 144.5 was adopted since it seemed probable that the error had consisted in recording a 3 instead of a 4. Unfortunately the subject had died before the error was suspected and could not be measured again.

Emma W, 26 years old, a sculptor's model. She was well proportioned, slightly above the average height and was neither fat nor thin. She had always been athletic and her muscles were well developed.

R H S, 21½ years old. An unusually tall and thin man who had lost about 5 pounds during the past year. For three days before his first measure-

ment an attempt was made to reduce his weight still further. He was kept for two days on a diet low in carbohydrates and salt. On the morning he was measured he took a light breakfast and played tennis for one and one half hours, drinking no water after the exercise.

Robert L., 43 years old. Five years previously he had lost both legs in a railroad accident. The right limb was cut off 50.5 cm below the superior border of the great trochanter, the left 25.5 cm below the same point. Both stumps were atrophied from disuse. His face, trunk and arms were fat.

Harry J., 34 years old, colored, usually called "Rubber tires" from the wheels on which he propelled himself with the velocity of a bicycle. His legs had been cut off in a railroad accident when he was only 6 years old. As a result of his deformity he had developed a form which reminded one of a hermit crab. The shoulders and arms were very large and powerful, the hips were those of an undeveloped boy, the stumps were atrophic. The left leg was cut off at the knee, the right about half way up the thigh. Six years previous to examination he had a stroke of apoplexy and the right side of the body was paralyzed, but was now spastic with some power of movement. As a result of this he propelled himself on his wheels and lifted himself about entirely with his left arm, which was unusually strong. He had no superfluous fat on his body.

#### METHODS USED

The area of the molds was determined by the method of printing on photographic paper and weighing described in Paper 5. In some of the cases, however, the molds were made by new methods, although the paper strip method previously described proved the most accurate and was used in all cases except when specifically noted. The cadaver of the baby, Anna M., was dressed in tight fitting clothing and melted paraffin applied to the whole surface. In the case of Fabian S. the tight fitting underclothing was covered with strips of surgeons' adhesive plaster and over this melted paraffin was painted. This same method was used in the first mold of Emma W. on May 3. It was noted that in both these cases it was comparatively easy to cut the mold open, while with the paper strip method it was hard to get even small probe-pointed scissors between the mold and the skin. This led to the suspicion that the adhesive plaster stretched, so the measurement of four of the parts was repeated with Emma W. Molds of the arm and leg were taken by the paper strip method on May 13, and of the trunk and thigh on May 17, measurements of the parts being made on the same day. The weight on May 3 was 58.09 kg, on May 13 57.22, on May 17, 57.62 kg. It will be seen in Table 3 that the paper method results were 6.5 per cent smaller for the arms, 8.6 per cent smaller for the thighs, 4.5 per cent smaller for the legs and 1.6 per cent larger for the trunk. When the totals for the four parts are compared, the paper results are 3.3 per cent lower, and it may be concluded that the data obtained by the adhesive plaster method in the case of Fabian S. are about 3.3 per cent too high and therefore should be excluded from the averages.

In all of these subjects the left upper and lower extremities were not included in the molds or in the measurements. In the case of Harry J, molds were made of the trunk and thighs alone, and with Robert L the mold of the head was omitted.

The measurements were made in the manner described in the previous paper and the same letters and numbers applied to them. In the previous work the measurement F was obtained by adding XIII and XIV, the distance from the tip of the olecranon to the lower border of the radius and from the olecranon to the outer end of the clavicle. These measurements had been made with the arm bent and their sum averages 9.5 per cent larger than the measurement from acromial process to lower border of the radius with the arm straight. Therefore, in using the formula the measurements should be made with the arm bent or else the factor 0.611 used instead of 0.558.

TABLE 3—COMPARISON OF AREAS OF PARTS OF BODY AS—

Name	Head			Arms			Hands		
	Measured	Formula	Error, %	Measured	Formula	Error, %	Measured	Formula	Error, %
Anna M	610	665	+9	456	403	-17	214	166	-28
F R S *	(1037)*	1031	(-0.5)	(1620)*	1475	(-9)	640	623	-3
Gerald S	950	978	+3	2152	2047	-5	876	875	-0
Emma W *	(1079)	1091	(+1)	(2402)*	2132	(-11)	806	683	-15
Emma W				2252	2145	-5			
R H S	1208	1197	-1	2778	2881	+7	891	1002	+12
Robert L		1196		2672	2313	-14	956	878	-8
Harry J		1104			2558				

\* Measured by adhesive plaster method, results average 3.3 per cent too high

ACCURACY OF METHOD

In order to give the method of measurement of the surface area a severe test, molds were made of a bowling ball, a perfect sphere with an average diameter of 21.78 cm and a calculated surface of 0.1490 square meters. The first mold was made by covering the ball with two layers of surgeon's gauze, pasting strips of paper over this, cutting off the mold and coating the inside with paraffin. The area of this mold was found to be 0.1566 square meters, or 5.1 per cent too large. A second mold was made with greater care. Only one thickness of gauze was used and this was drawn over the ball like a bag, the excess being trimmed off. The paper strips were pasted very tight and the paraffin omitted. The area of the second mold was 0.1488 square meters, or

0.13 per cent lower than the theoretical surface area. This shows that the method is accurate if the paper be applied very tightly in the manner always used by us, but that if the strips be applied at all loosely or if a material such as adhesive plaster be used, there may be a plus error of 3 to 5 per cent.

One criticism of the linear formula which has been made is that it would be difficult for two observers to obtain concordant results on the same individual. To test this point a man 182.8 cm tall, weighing 87.08 kg, was measured by two of the staff independently and the surface calculated according to the "Linear Formula." The first result was 2.0733 square meters, the second 2.0798, the difference being 0.3 per cent. Another subject was measured independently by two physicians, one of whom had never seen the method applied, and the results agreed within 0.5 per cent. This is probably closer agreement

ACTUALLY MEASURED AND AS CALCULATED FROM FORMULAS

Trunk		Thighs			Legs			Feet		
Formula	Error, %	Measured	Formula	Error, %	Measured	Formula	Error, %	Measured	Formula	Error, %
1347	-1	478	488	+2	340	318	-7	216	205	-5
3978	(-3)	(2166)*	2130	(-2)	(1456)*	1407	(-3)	(834)*	808	(-3)
5165	+3	3002	2677	-11	1870	2144	+14	1042	1055	+1
5482	(-1)	(3608)*	3424	(-5)	(2392)*	2030	(-15)	(1084)*	1032	(-5)
5522	-2	3324	3448	+4	2288	2207	-4			
5867	-3	3155	3457	+9	2634	2587	-2	1251	1301	+4
7701	+12	1755	1781	+1						
6130	-7	{ 794 1196	Right Left							

than would often be found, since measurements of the same part made by one man sometimes differ by 5 per cent. There is no factor except a difference in the tension of the tape which would throw the error in one direction more often than the other.

#### DISCUSSION OF RESULTS

Tables 1 and 2 give the linear measurements, and Tables 3 and 4 the results of the determinations of the surface area. The individual parts show a somewhat greater divergence between the area as determined by formula and as actually measured than in the former paper, but this was to be expected. The total results are all that could be desired. In the cases of Gerald S. and R. H. S. the errors in the

formula are 0.3 and 0.1 per cent, respectively. With Anna M. and with Emma W. as measured by the paper method, —2.9 and —2.0 per cent. The average error for these four subjects is 1.3 per cent. Fabian S. shows an apparent error of 3.5 per cent when measured by the adhesive plaster method. This would be reduced to —0.2 per cent if we made the correction for the average plus error of 3.3 per cent in the adhesive method.

TABLE 4—SUMMARY

Name	Surface Area		Error, %	Surface Area, Meeh's For- mula	Error, %	Cor- rect Con- stant Meeh's For- mula	Age, Yrs	Weight, Kg	Height, Cm
	Mea- sured	Linear For- mula							
Anna M.	0.3609	0.3592	—2.9	0.405*	+9.3	10.9	2	6.27	73.2
F. R. S.	(1.1869)†	1.1455	(—3.5)	1.260	(+6.2)	(11.6)	12	32.74	141.5
Gerald S.	1.4901	1.4941	+0.8	1.563	+4.9	11.7	17	45.25	171.8
Emma W.	(1.6897)†	1.5874	(—6.0)				26		
Emma W.	1.8451	1.6128	—2.0	1.837	+11.6	11.0	26	57.62	164.8
R. H. S.	1.7981	1.7993	+0.1	1.949	+8.4	11.4	21	63.00	184.2
Robert L.	1.4209	1.4692	+2.7	1.960	+37.0			63.81	
Harry J.		1.3054		1.800	+28.0			55.92	

\* Constant used for Meeh's formula for the baby = 11.9, for adults 12.3

† Measured by adhesive plaster method, results average 3.3 per cent too high

## SUMMARY AND CONCLUSIONS

The so-called "Linear Formula" for the estimation of the surface area has been satisfactorily tested on four new subjects of varying size and shape. In addition, partial measurements of two legless men have been made. The average error in the formula when applied to the four subjects was 1.3 per cent. Two of the subjects were children and in these cases the error in the formula was under 3 per cent. Since the youngest was about 2 years old it does not seem advisable to use the formula for babies under this age until the factors have been tested by the measurements of infants.

In conclusion we wish to thank Dr. A. L. Meyer and Mr. G. F. Soderstrom for their aid in making the molds and measuring the subjects.

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# CLINICAL CALORIMETRY

## TENTH PAPER

### A FORMULA TO ESTIMATE THE APPROXIMATE SURFACE AREA IF HEIGHT AND WEIGHT BE KNOWN\*

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Since the publication of Paper 5 of this series the so-called "Linear Formula" has been used in the study of a large number of individuals. Practically all of the subjects of respiration experiments in the Sage calorimeter have been measured in this way, and in addition Means<sup>1</sup> of Boston has used it as a factor in determining his normal base line of metabolism and the extent of the pathological variations. Means has found that the range of normal variation from the average is smaller and that the apparent depression of metabolism in obesity is much less marked when the linear formula, instead of Meeh's formula, is used to determine surface area.

The accuracy of the linear formula has been shown in Paper 9 of this series. In order to correct the slight error in the factor for the arms, and also in order to clear up a few points in the measurements which may cause confusion, it seems best to repeat the formula and show the bony landmarks by diagram (Fig 1). Some difficulty has been experienced in locating the superior border of the great trochanter in fat subjects. This landmark is the starting point of the measurement "O" which represents the length of the thighs. If we employ another factor we can use the new measurement "W," the distance from lower border of the patella to the upper border of the pubes, a point already located in the measurement "L". In taking this measurement, however, one must be careful to have the legs straight and the knees, heels and great toes touching. It is better to take all measurements from a footboard with the subject lying down,<sup>2</sup> determining distance from soles of feet to lower border of patella, to upper border of

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\* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital

1 Means, J H. Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour Med Research, 1915, xxxii, 121; Basal Metabolism and Body Surface, Jour Biol Chem, 1915, xxi, 263

2 This is especially important with obese patients



pubes, to suprasternal notch and to top of the head In Table 1 a comparison is made of the old and new formulas for determining the surface of the thighs It is seen that the average error is the same

In the literature of the work on respiratory metabolism it has been customary to give only the age, weight and height If, therefore, we

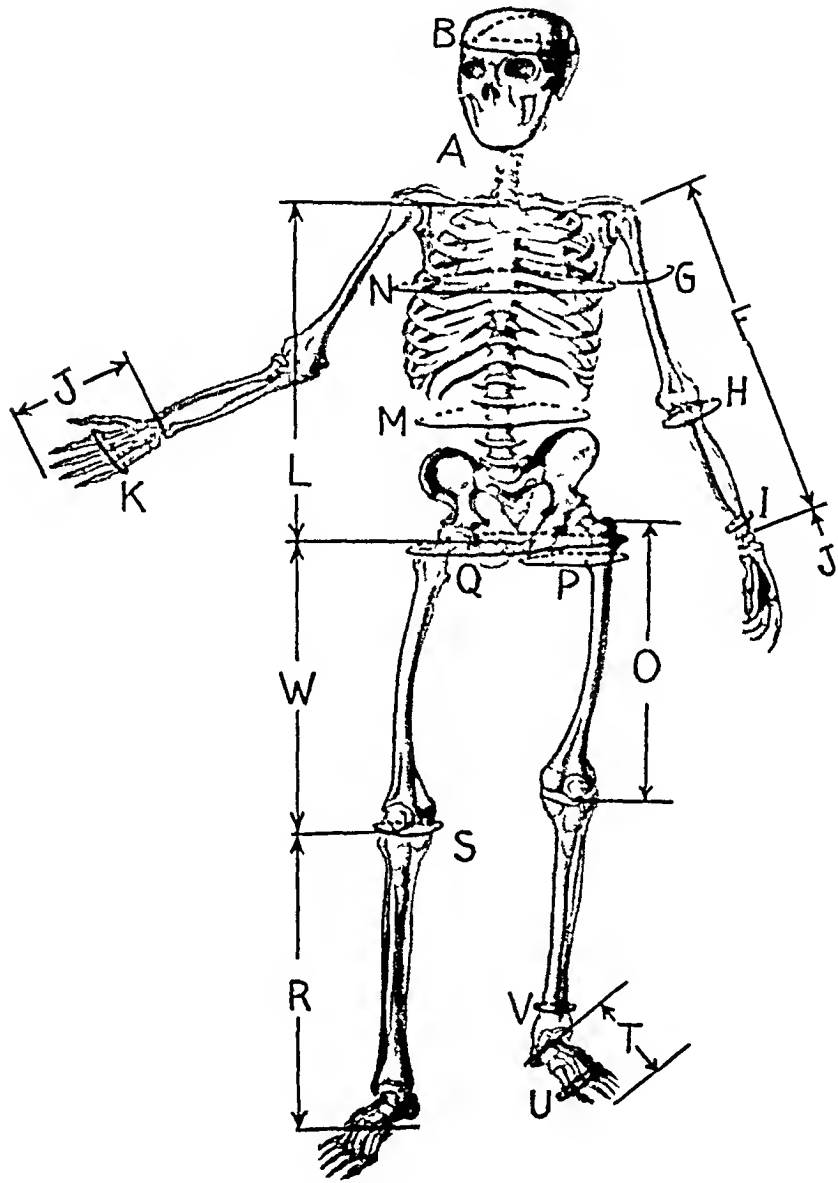


Fig 1—Measurements used in "Linear Formula"

are to recalculate previous work in an effort to get more accurate results than are furnished by Meeh's formula we must content ourselves with calculations based on height and weight A formula such as Meeh's, based on weight alone, can easily give an error of 15 to 20 per cent ,

3 Dr F G Benedict of Boston has called our attention to the fact that this determines the length rather than the height We have found that as a rule the length is 1 or 2 centimeters greater than the height, but we must remember that height varies 1 to 3 centimeters during the day

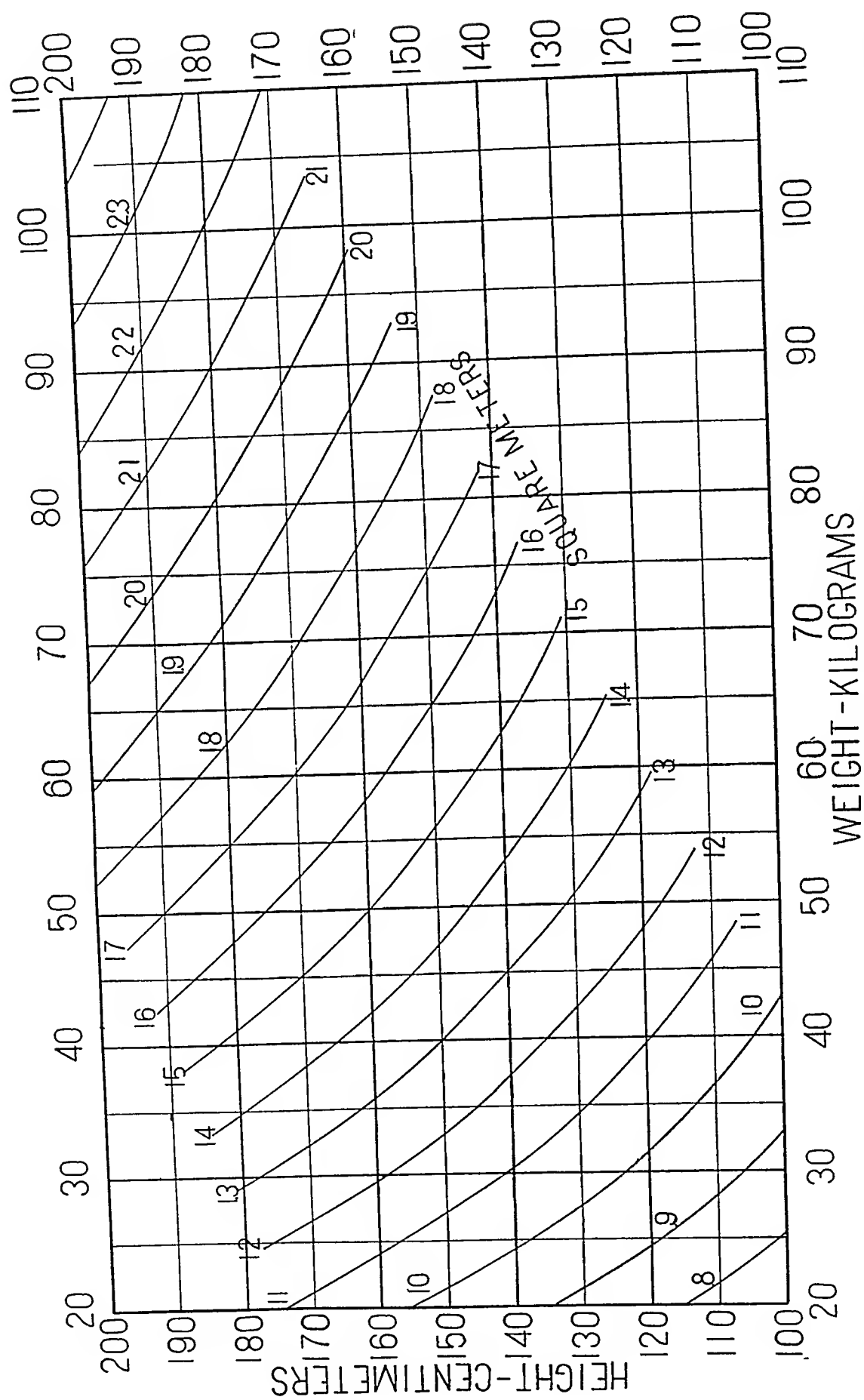


Fig 2—Chart for determining surface area of man in square meters from weight in kilograms (Wt) and height in centimeters (Ht) according to the formula  $\text{Area (Sq Cm)} = \text{Wt}^{0.423} \times \text{Ht}^{0.725} \times 71.84$

but this error is greatly reduced by taking the height into consideration. With people of very unusual body shape there does not seem to be any accurate method simpler than the linear formula with its nineteen measurements. The reason why a consideration of the height does not entirely correct the calculations based on weight becomes apparent when we consider the circumference of the body at various levels. For instance, in the case of R. H. H. the average circumference of the legs was 30.0 cm and of the thighs 43.9 cm. An increase of 10 cm in the length below the knees would mean an increase of 600 sq cm in surface area, but if the length of the thighs were increased 10 cm it would mean a gain of 878 sq cm. Variations in the arms would not affect the height at all.

TABLE 1—COMPARISON OF OLD AND NEW FORMULAS FOR DETERMINING SURFACE AREAS OF THIGHS

Name	Thigh Measurement*		Surface Thighs as Meas., Sq. Cm.	Surface Calc. O(P+Q) 0.508	Error, %	Surface Calc. W(P+Q) 0.532	Error, %
	"O" Om.	"W" Om.					
Benny L.	26.4	22.4	1284	1294	+1	1195	-7
Morris S.	41.7	38.8	3022	3207	+6	3251	+7
R. H. H.	47.0	46.0	3712	3712	-5	3745	+1
E. F. D. B.	46.3	46.3	3820	3635	-4	3981	+4
Mrs. McK.	40.0	32.2	3500	3594	+3	3152	-11
Anna M.	16.0	14.4	478	488	+2	479	+0
Gerald S.	44.7	44.9	3002	2677	-11	2927	-3
Fenna W.	45.7	41.7	3824	3448	+4	3425	+3
R. H. S.	50.8	46.8	8175	8457	+9	8464	+9
Average					±5		±5

\* Old measurement "O," superior border of great trochanter to lower border of patella.  
New measurement "W," superior border of pubes to lower border of patella.

A formula to express surface area must naturally be a bi-dimensional formula, as surface involves two dimensions. If we assume that weight is proportional to volume, it is obvious that three dimensions are involved in any expression for weight. Height is, of course, a single dimension. If we attempt to construct a formula for surface area (A) based on weight (W) and height (H), it is obvious that a simple formula such as  $A = W \times H \times C$  (C being a constant depending on the units used and the subject to which the formula is to apply) is not logical. In this formula one side, A, is bidimensional and the other side,  $W \times H \times C$ , involves four dimensions, three from W and one from H. If W is tridimensional, it is obvious that the cube

root of  $W$  ( $=\sqrt[3]{W}$  or  $W^{1/3}$ ) is undimensional and a formula  $A = W^{1/3} \times H \times C$  is logical in that it is bidimensional on both sides. Another bidimensional expression involving  $W$  and  $H$  would be the square root of  $W \times H$  ( $\sqrt{W \times H}$  or  $W^{1/2} \times H^{1/2}$ ) because  $W \times H$ , being four-dimensional, is reduced to a bidimensional expression on taking the square root. A formula based on this method of reduction would be  $A = W^{1/2} \times H^{1/2} \times C$ .

TABLE 2—MEASUREMENTS AND CONSTANTS FOR LINEAR FORMULA (MEASUREMENTS TAKEN WITH SUBJECT LYING ON A FLAT SURFACE)

HEAD AB 0 308

A—Around vertex and point of chin

B—Coronal circumference around occiput and forehead, just above eyebrows.

ARMS F(G + H + I) 0 611 \*

F—Tip of acromial process to lower border of radius, measured with forearm extended

G—Circumference at level of upper border of axilla

H—Largest circumference of forearm (just below elbow)

I—Smallest circumference of forearm (just above head of ulna)

HANDS JK 2 22

J—Lower posterior border of radius to tip of second finger

K—Circumference of open hand at the meta-carpo-phalangeal joints

TRUNK (Including neck and external genitals in the male, breasts in female):

L(M + N) 0 703

L—Suprasternal notch to upper border of pubes

M—Circumference of abdomen at level of umbilicus

N—Circumference of thorax at level of nipples in the male and just above breasts in the female

THIGHS O(P + Q) 0 508

O—Superior border of great trochanter to the lower border of the patella

P—Circumference of thigh just below the level of perineum

Q—Circumference of hips and buttocks at the level of the great trochanters

Or —THIGHS W(P + Q) 0 552

W—Upper border of pubes to lower border patella (measured with legs straight and feet pointed anteroposteriorly)

P—As above

Q—As above.

LEGS RS 1 40

R—From sole of foot to lower border of patella

S—Circumference at level of lower border of patella

FEET T(U + V) 1 04

T—Length of foot including great toe

U—Circumference of foot at base of little toe

V—Smallest circumference of ankle (just above malleoli)

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> Factor 0 558 if F is measured over olecranon with forearm flexed

NOTE—The constants for arms, thighs, etc., when multiplied by the measurements of one side give the surface area for both sides. To find total surface area add the seven parts

TABLE 3—COMPARISON OF VARIOUS FORMULAS

Name	Weight, kg.	Height or Length, Cm.	Measured or Deter- mined by Linear For- mula Area, Sq Cm.	Area = C		Area = C		Area = C	
				$\frac{\text{Area}}{\text{Ht} \times \text{Wt}}$		$\frac{\text{Area}}{\sqrt{\text{Ht}} \times \text{Wt}}$		$\frac{\text{Area}}{\frac{1}{\text{Wt}^{2.75}} \times \frac{1}{\text{Ht}^{1.75}}}$	
				Factor C	Varia- tion from 256, %	Factor C	Varia- tion from 167.2, %	Factor C	Varia- tion from 71.84, %
Measured by Molds									
Benny L	24.2	110.3	8473	26.7	+4.3	161.0	-2.0	72.50	+0.7
Morris S	61.0	161.3	16720	25.5	-0.5	167.0	-2.5	70.65	-1.6
R. H. H.	64.1	178.0	18975	27.8	+0.8	171.5	+2.6	73.22	+1.9
E. F. D. B.	74.1	170.2	10000	25.3	-1.2	164.7	-1.5	70.85	-1.3
Mrs. McK.	93.0	149.7	18592	27.2	+6.2	157.5	-5.8	71.70	-0.2
Gerald S.	45.2	171.8	11901	24.1	-1.7	169.2	+1.2	70.36	-2.0
Fab. S.	32.7	141.5	(11869)*	25.5	(-0.5)*	174.2	(+4.0)*	74.37	(+3.5)*
Anna M.	62.7	73.2	3699	27.4	+7.1	172.0	+3.0	75.71	+5.1
Emma W.	57.6	164.8	16151	25.8	+0.8	169.0	+1.1	72.56	+1.0
R. H. S.	63.0	184.2	17081	24.5	-4.3	167.0	0.0	70.58	-1.7
Average					+3.3		+2.2		+1.7
Measured by Linear Formula									
Ldw. B.	62.3	174.0	17270	25.0	-2.3	165.2	-1.2	70.75	-1.5
John K.	65.4	170.0	17610	24.9	-2.7	164.2	-1.7	70.83	-1.4
Alb. S.	66.4	162.2	16720	25.5	-0.5	161.0	-3.7	70.20	-2.3
Wm. S.	44.6	179.0	15470	23.7	-7.4	172.8	+3.3	71.53	-0.4
A. F. C.	69.6	179.4	17960	24.4	-1.7	160.5	-4.0	68.71	-4.4
Wm. A.	63.4	180.0	17940	24.9	-2.7	168.2	+0.6	71.22	-0.8
Mart. C.	44.0	166.8	14370	24.5	-4.3	167.5	+1	70.44	-1.9
Ios. U.	40.1	179.0	14520	23.7	-7.4	171.2	+2.3	70.36	-2.1
Wm. Shee.	63.8	171.0	16070	23.5	-8.2	174.8	-7.5	66.06	-8.0
Arthur V.	58.3	155.0	15500	25.8	+0.8	163.3	-2.4	73.02	+1.6
Arnon W.	60.8	161.0	15500	23.6	-7.8	176.6	-6.1	67.96	-5.4
Annie T.	26.3	137.0	10460	25.6	0.0	174.0	+4.1	73.60	+2.4
Fred D.	49.3	157.0	13870	24.1	-5.8	177.2	-6.0	67.69	-5.7
Fred D.	40.0	157.0	12960	24.2	-5.5	163.5	-2.3	69.12	-3.8
Edw. T.	50.4	168.0	14830	23.4	-8.6	161.0	-3.7	68.27	-5.0
J. McE.	41.8	166.0	13260	23.1	-9.7	159.0	-4.8	66.67	-7.2
Bart D.	43.5	156.0	13850	25.3	-1.2	168.1	+0.5	71.62	-0.3
Burr Ph.	70.7	169.0	17390	24.9	-2.7	159.0	-4.8	69.01	-3.9
J. D. D. B.	34.5	152.8	12240	24.7	-3.5	168.6	+0.7	70.90	-1.3

TABLE 3—(Continued)

Name	Weight, kg	Height or Length, Cm	Measured or Deter- mined by Linear For- mula, Area, Sq Cm	Area = C $\frac{Ht}{\sqrt{Wt}}$		Area = C $\frac{1}{\sqrt{Ht} \times \sqrt{Wt}}$		Area = C $\frac{1}{Wt^{2/35} \times Ht^{1/38}}$	
				Factor C	Vari- ation from 25.6, %	Factor C	Vari- ation from 167.2, %	Factor C	Vari- ation from 71.84, %
Ray M	30.4	140.5	10840	24.8	-3.1	165.8	-0.8	70.42	-1.9
Harry B	36.5	146.0	12320	25.4	-0.8	168.6	+0.8	72.01	+0.3
Harry K	35.9	148.2	12240	25.0	-2.3	167.8	+0.2	71.30	-0.8
Arthur A	30.6	146.6	11260	24.6	-3.9	167.0	-0.1	70.71	-1.6
Leslie B	28.5	140.8	10500	24.5	-4.3	166.5	-0.5	70.00	-2.6
Peter N	63.4	187.7	17950	24.0	-6.2	164.2	-1.8	69.09	-3.8
Max W	73.2	173.7	18540	25.5	-0.5	164.5	-1.7	71.07	-1.1
Dan O'C	60.0	167.0	16570	25.4	-0.8	165.7	-1.0	71.12	-1.0
Jack O'C	31.4	162.8	12040	23.5	-8.2	168.2	+0.6	69.35	-3.5
A F	52.6	159.0	14870	25.0	-2.3	162.5	-2.9	69.95	-2.6
G L	79.2	175.5	20300	26.9	-5.1	172.2	+3.0	74.70	+4.0
F C G	56.5	173.9	16440	24.7	-3.5	167.4	0.0	70.29	-2.1
L M	59.5	170.6	16340	24.6	-3.9	162.1	-3.0	69.30	-3.5
F G B	87.1	182.8	20760	25.8	-0.8	164.5	-1.1	71.22	-0.9

\* Measured by adhesive plaster method which gives results about 33 per cent too high. The plus variations would be reduced by this amount.

Comparing the two formulas  $A = W^{1/3} \times H \times C$  and  $A = W^{1/2} H^{1/2} \times C$ , it will be seen that they differ in the relative importance given to W and H. In the former W has less importance and H more importance than in the latter. Meeh's formula  $A = W^{2/3} \times C$ , failed because H was neglected entirely. Adding H to the formula makes it more nearly applicable to subjects of the same general shape but differing somewhat in relative dimensions, and the best formula involving only W and H will be the one which gives a certain best relative importance to W and H.

Both of the above formulas were carefully investigated by applying them to the nine subjects that had been measured in the laboratory. For these subjects W, H<sup>4</sup> and A are known. In testing a formula the procedure was to solve for C (the only unknown) for each of the ten cases and then to assume the correct constant for the formula to be the average value of the C's so found. The merit of the

4 With about half the subjects this was determined standing. No attempt has been made to correct for the difference between height and length. (See Footnote 3, p. 864.) The largest difference we have found would cause a change of about 1.5 per cent in the surface area and reading. This is within the limit of accuracy claimed for the Height-Weight Chart.

formula was then judged by the percentage variation of the factors C, as found for the individual cases, from the constant chosen. This percentage variation would also be the percentage error in area in the individual cases if the formula were applied using the chosen constant.

The formulas with  $H^1$  and  $H^{1/2}$  both gave rather good results, but it was noticed in a number of cases that the percentage error for the same subject differed in sign for the two formulas. This would indicate that some formula would be better than either of these two if H were raised to some power between  $1/2$  and 1.

The formula  $A = W^{1/3} \times H \times C$  can also be written  $A = W^{1/3} \times H^{1/1} \times C$ , bringing it into the same form as  $A = W^{1/2} \times H^{1/2} \times C$  and the general form of this formula can be written  $A = W^{1/a} \times H^{1/b} \times C$ . In order that the expression  $W^{1/a} \times H^{1/b} \times C$  may remain bidimensional it is only necessary that  $3/a \times 1/b = 2$ , as it does in the two cases considered. For an intermediate equation it is obvious that (b) must be greater than 1 but less than 2. A value of  $b = 1.25$  would give  $a = 2.5$  and the formula would be  $A = W^{1/2.5} \times H^{1/1.25} \times C$ . This formula when tested gave very much better results than either of the others, but to find the best values of "a" and "b" it was necessary to explore formulas having a number of other combinations of "a" and "b" and then to interpolate graphically.

The best values of "a" and "b" were found to be  $a = 2.35$  and  $b = 1.38$  giving the formula the final form of  $A = W^{1/2.35} \times H^{1/1.38} \times C$  or  $A = W^{0.425} \times H^{0.725} \times 71.84$ . This formula can be solved by logarithms as follows:

$$\text{Log } A = \text{Log } W \times 0.425 + \text{Log } H \times 0.725 + 1.8564$$

1.8564 is a constant equal to  $\text{Log } C$ .

In order to make this somewhat complicated formula easy of application a chart has been constructed (Fig. 2). By means of this it is possible to find the approximate surface area at a glance. The ordinates represent the height in centimeters, the abscissae the weight in kilograms. The point of intersection of these lines is found for any given subject and the surface area in square meters read off on the curved lines by interpolation. The second decimal place, which is never accurate, is estimated by the distance of the point from the nearest curved line. For instance, if the man were 150 centimeters tall and weighed 60 kilograms, the approximate surface area would be 1.55 square meters.

The large plus error in the constant employed by Meeh<sup>5</sup> has been established by the previously quoted works of Bouchard, Lissauer, Sicheff, Lassabliere and ourselves. According to our calculations the

5 Meeh. *Ztschr. f. Biol.*, 1879, xv, 425.

average error in Meeh's constant is about 15 per cent. Instead of a uniform figure of 12.312, the "constant" should average about 10.5, varying between 12.3 for the greatly emaciated and 9.0 for the very stout. We must remember that figures for the calories per square meters of body surface will average 15 per cent. smaller when Meeh's formula is used than when the linear formula or the new Height-Weight Formula" is employed.

#### SUMMARY AND CONCLUSIONS

The method of calculating the surface area from the so-called "Linear Formula" is given with a slight correction in the factor for the arms and an alternative measurement for the thighs. A simpler "Height-Weight Formula" has been devised to estimate the surface of subjects if only their height and weight be known. This is expressed in the terms  $A = W^{0.425} \times H^{0.725} \times C$ , A being the surface area in square centimeters, H the height in centimeters, W the weight in kilograms and C the constant, 71.84. A chart has been plotted from this formula so that the approximate surface area may be determined at a glance.

We may estimate the errors in the various formulas as follows: "Linear Formula" and "Height-Weight Formula," maximum  $\pm 5$  per cent., average  $\pm 1.5$  per cent.; Meeh's Formula, maximum  $+ 30$  per cent., average  $+ 15$  per cent. In general the maximum figures apply only to those of unusual shape, while with those of average body form the average error will seldom be exceeded.

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# CLINICAL CALORIMETRY

## ELEVENTH PAPER

### A COMPARISON OF THE METABOLISM OF MEN FLAT IN BED AND SITTING IN A STEAMER CHAIR \*

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AND

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This paper and those which follow it are based on results obtained with the Sage calorimeter, which was described a year ago in the first two papers of the series. At that time the policy was adopted of publishing all the alcohol checks to show the accuracy of the apparatus throughout the year. It gives considerable satisfaction to report that the uniformly good results previously obtained have been repeated in this, the third season in which the calorimeter has been used. After a period of several weeks needed to put the apparatus in order, a good check was made Oct 22, 1914, and not till then were the experiments begun. Although there was no reason to suspect trouble with the apparatus, tests were made Nov 28, 1914, Jan 1, 1915 and also on May 19, 1915, after the last experiment for the season was completed. The results are recorded in Table 1 in which it will be seen that the total errors were as follows: heat, + 0.51 per cent, oxygen — 0.51 per cent, carbon dioxide — 0.36 per cent, water + 3.13 per cent. The respiratory quotient averaged 0.666, while the theoretical quotient is 0.6667.

Since the publication of Paper 2<sup>1</sup> a new valve has been designed by one of the authors (G F S) and has been attached to the absorber table, with most satisfactory results. The three-way valves by means of which the air current was switched from one set of absorbing bottles to the other required constant attention to prevent leaks. The new valves have been used in about ninety experiments and have required repairs but once. The details are shown in Figure 1.

The calorimeter bed has been the subject of much experimentation. The oak frame on skids has proved satisfactory from the start, but the springs under the subjects sagged too much and the blanket covering

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<sup>1</sup> From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital

1 Riche and Soderstrom. Chemical Calorimetry, Paper 2, THE ARCHIVES INT MED, 1915, xv, 805

the springs stored too much heat. A waterproof canvas, substituted for the springs, was more comfortable, but heat was accumulated underneath the subject and was suddenly liberated whenever he moved. This made the heat control difficult. During the last year a comfortable hammock made of fish net has given excellent results. Comparatively little heat is banked up underneath the man and when he turns over the liberation of heat is only one half or three quarters as great as in previous years to judge from the expansion of air in the box. This means that a given reading on the work-adder in the season of 1914-1915 indicates a little more activity on the part of the subject than the same reading in previous years.

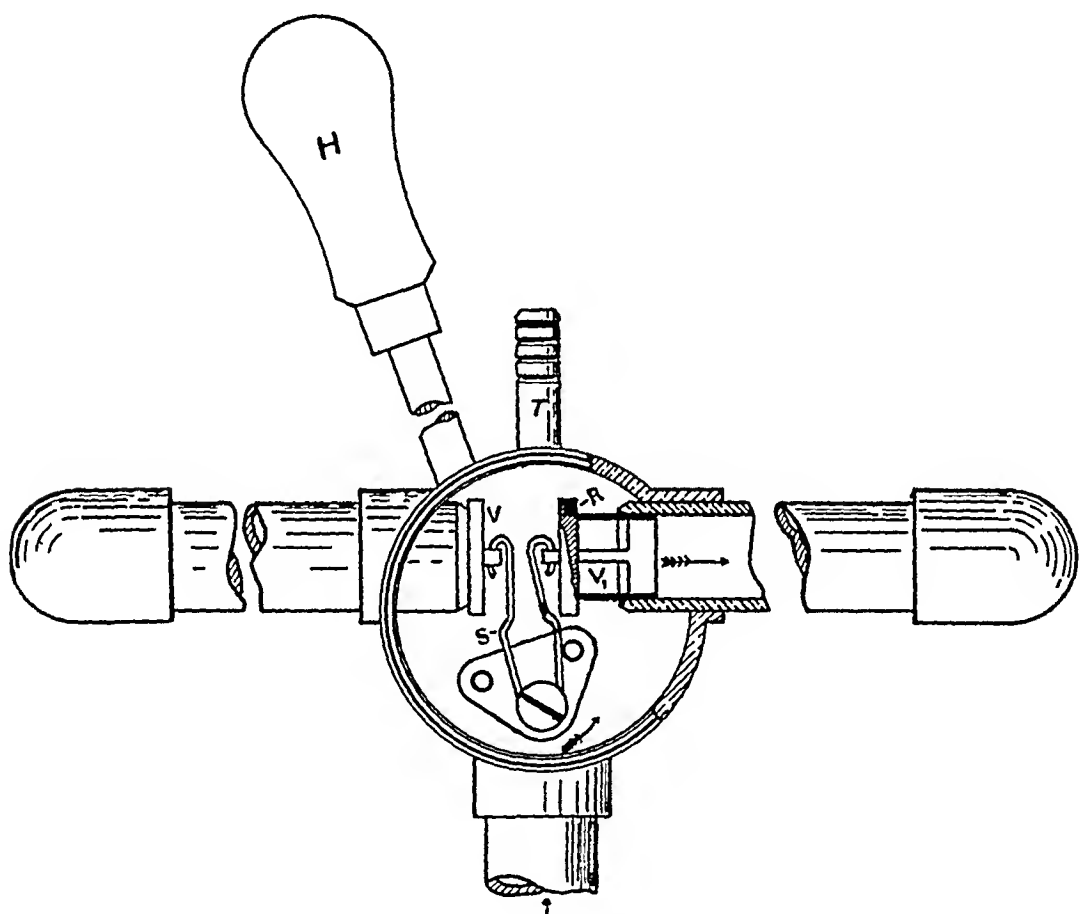


Fig 1—Double throw valve for absorber table. H, handle, T, tube through which sample of air can be removed, S, piano wire spring to open and close valves V and V<sub>1</sub>, R, rubber washer acting as seat for valve.

Figure 2 shows the bed with the oak frame and hammock. Figure 3 shows the steamer chair used after Jan 8, 1915. It is very comfortable for the average subject, and even some of those who were not orthopneic preferred it to the bed.

In recording the movements of the spirometer at the close of each hour we have used a pen (Fig 4) which enables us to dispense with smoked paper. A glass tube a little more than 2.5 cm long and 9 mm in diameter is sealed at one end. The other end is closed by means of

cork and sealing wax, through which passes a fine capillary tube bent at a right angle. The capillary passes nearly to the bottom of the tube. The tube is filled with ink, containing a little glycerin. This simple apparatus seems to work even better than the expensive article of commerce which has a platinum tube.

When the calorimeter was planned it was built high enough at one end to allow a man to sit upright. This was essential if orthopneic, cardiac or nephritic patients were to be studied. It soon became evident

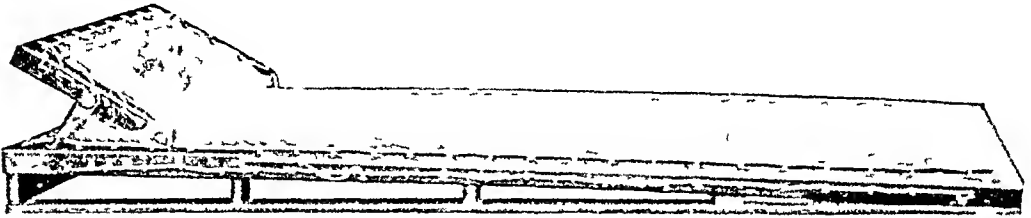


Fig 2—New calorimeter bed

that normal subjects should be studied while lying flat and also while sitting with a back rest to serve as controls. The form and accuracy of the Sage calorimeter seemed to lend itself particularly well to this investigation, which requires a greater delicacy of technic than has previously been available.

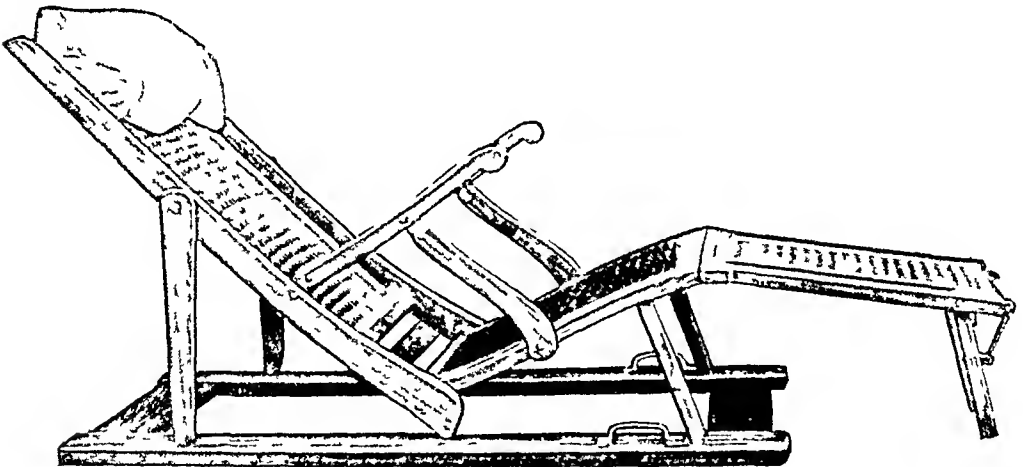


Fig 3—Steamer chair for calorimeter

Katzenstein<sup>2</sup> in 1891 found that the metabolism of his subjects was higher when standing than when lying and that the increase was comparatively slight if the man were standing in a comfortable relaxed position. Winternitz and Pospischil<sup>3</sup> found the carbon dioxide output

2 Katzenstein, G. Ueber die Einwirkung der Muskeltätigkeit auf den Stoffwechsel der Menschen, *Arch f d ges Physiol*, 1891, xlix, 330.

3 Winternitz and Pospischil. Ueber den respiratorischen Stoffwechsel unter thermischen und Mechanischen Einflüssen, *Bl f klin Hydrotherapie*, 1893, 3, 7, 30, 49, 62.

lowest while lying, higher while sitting and still higher while standing. Some of their quotients are so low as to suggest doubts as to the technic. Johansson<sup>4</sup> determined the carbon dioxide production with scrupulous care to avoid the disturbing influences of muscular movement. He found that the output was about 6 per cent higher while sitting than while lying, but he gives no details as to the exact postures used. Widlund<sup>5</sup> found no apparent rise in metabolism when the man stood if the muscular relaxation were complete. Benedict and Carpenter<sup>6</sup> have compared the metabolism of their subjects in two different calorimeters. Their bed calorimeter is smaller than the Sage instrument and the subjects lie flat during the experiments, are very quiet and often go to sleep. Their chair calorimeter contains a comfortable arm-chair, tilted slightly backwards but without a head rest. In this chamber the subjects are not absolutely quiet, but are allowed to read. The

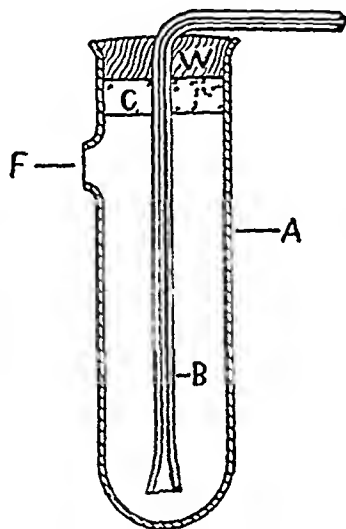


Fig 4—Capillary writing pen. A, glass reservoir for ink, F, opening for filling, C, cork, W, sealing-wax, B, capillary glass tube.

matter is critically treated by Benedict and Joslin,<sup>7</sup> who conclude that the increase in metabolism of a subject while sitting in a chair and awake over that when lying asleep varies from 20 to 30 per cent. The question was further studied by Emmes and Riche<sup>8</sup> in the same labora-

4 Johansson, J. E. Ueber den Tageschwankungen des Stoffwechsels und der Körpertemperatur im nüchternen Zustand und vollständigen Muskelruhe, *Skand Arch f Physiol*, 1898, viii, 85.

5 Widlund, K. E. Untersuchung des Verhältnisses zwischen CO<sub>2</sub> Produktion in Ruhelage und im stehenden Stellung, *Skand Arch f Physiol*, 1905, xvii, 290.

6 Benedict and Carpenter. *Metabolism and Energy Transformation of Healthy Man During Rest*, Carnegie Institution of Washington, Pub 126, 1911, p 242.

7 Benedict and Joslin. *Metabolism in Diabetes Mellitus*, Carnegie Institution of Washington, Pub 136, 1910, p 175.

8 Emmes, L. E., and Riche, J. A. The Respiratory Exchange as Affected by Body Position, *Am Jour Physiol*, 1911, xxvii, 406.

tory, using the Benedict Universal Respiration Apparatus to which the subjects were attached by means of nose pieces. They found the oxygen consumption averaged 76 per cent higher when they were sitting upright in a chair with the head supported than when lying flat. This they considered due primarily to the difference in the internal muscular activity necessitated by the sustaining of body parts. They call attention to the fact that the pulse rate is 5 to 10 per cent higher when sitting. Higgins,<sup>9</sup> also of the Nutrition Laboratory, studied the effect of posture on the tension of carbon dioxide in the alveoli, and found it highest with the subject lying on his back or side, lower in the Trendelenburg and semireclining position, still lower while sitting erect and lowest while standing.

#### DESCRIPTION OF SUBJECTS OF EXPERIMENTS

John L., 44 years old, 1747 cm tall, normal control, history given in Paper 4.<sup>10</sup> March 26, 1914, he lay flat on the canvas bed. April 3 he sat propped up in bed at an angle of about 50 degrees, leaning against a firm back rest, padded with pillows, which supported his head.

Albert G., 24 years old, 1622 cm tall, normal control. He is a laborer, born in Italy. He remembers no illnesses except a slight skin eruption fourteen years ago. His health is good but he has been out of work for some time. He is short, stocky, fairly muscular, with little fat. Heart and lungs normal. Admitted to the metabolism ward Dec 14, 1914, discharged Jan 14, 1915. From January 4 to 14 he had a very mild sore throat, with slight afternoon fever. January 13 at 10 a. m., he was given subcutaneously a dose of New York City Board of Health typhoid vaccine consisting of one-half billion dead bacilli. There was a slight normal reaction with moderate swelling at the site of injection.

The young Italian was rather neurotic, and after a couple of weeks of enforced idleness in the ward began to develop imaginary pains. He left the hospital in high dudgeon, but when his wages were spent in the course of the next two weeks he returned asking for his job as normal control.

December 21, lying flat in bed, he was unusually quiet, sleeping twenty-four minutes in the first hour and about six minutes in the second. Two days later, propped up at an angle of about 45 degrees with the back rest, he was not so quiet. The third period had to be discarded from the calculations because he slid down in the bed until the body was at about half its original angle. December 28 he was in the calorimeter for two periods, each one and one-half hours long. He was lying flat and very quiet, dozing most of the time. December 30 an experiment was made after the ingestion of 79 gm of olive oil. January 4 and 6 tests were made after 115 gm commercial glucose. On the eighth a three hour basal determination was made. He slept fifty-five minutes in the first hour and was somewhat restless in the other hours. The next day he was in the calorimeter, sitting in the steamer chair which had just been finished. In the first hour he was somewhat restless, in the second hour quiet. Unfortunately the urine specimen was lost on this day.

R. H. S., man, 21½ years old, chemist, normal control. Except for measles, scarlet fever and a broken arm in childhood he has never been sick in bed. He

9 Higgins, H., L. The Influence of Food, Posture and Other Factors on the Alveolar Carbon Dioxide Tension in Man, *Am Jour Physiol*, 1914, *LXXIV*, 114.

10 Gephart and DuBois. Clinical Calorimetry, Paper 4, *THE ARCHIVES INT MED*, 1915, *xv*, 835.

TABLE 1—ALCOHOL CHUCKS

Date	Run	Hydro				Oxygen			Carbon Dioxide			Water			R Q Theory, (0.007)
		Alcohol burned, Gm *	Theory, Cal	Found, Cal	Error, %	Theory, Gm	Found, Gm	Error, %	Theory, Gm	Found, Gm	Error, %	Theory, Gm	Found, Gm	Error, %	
10/02/11	1	12.22	78.11	77.14	-1.2	23.02	22.56	-1.9	20.01	20.92	-0.8	14.52	15.32	-10.8	0.672
	2	11.90	76.85	75.19	-1.6	22.52	22.77	1.1	20.61	20.11	-1.1	13.91	14.60	-15.7	0.652
	3	11.94	76.99	75.17	-1.0	22.17	21.55	-2.7	20.59	20.25	-1.6	13.81	14.99	-11.7	0.671
Average . .		...	76.97	75.92	-1.3	22.69	22.89	-1.3	20.77	20.53	-1.1	13.52	14.70	-16.8	0.668
11/07/11	1	11.96	76.19	77.71	1.6	22.52	22.17	-1.5	20.61	20.55	-0.1	13.91	14.11	-12.1	0.671
	2	12.23	78.21	78.36	10.2	23.03	23.01	-0.0	21.11	21.06	-0.2	14.15	14.10	-10.2	0.661
	3	12.56	80.32	80.81	10.6	23.65	23.40	-1.0	21.08	21.17	-0.0	14.53	14.60	-10.1	0.667
Average . . .		.	78.91	78.98	10.8	23.07	22.87	-0.8	21.11	21.09	-0.5	14.17	14.31	-11.0	0.668
1/18/15	1	13.07	87.11	89.35	12.2	25.71	25.89	10.0	24.60	23.10	-1.7	15.82	16.31	-13.2	0.652
	2	13.51	89.58	88.99	-1.2	25.50	25.81	11.2	23.87	24.51	10.7	15.67	16.27	-13.8	0.669
	3	13.62	87.09	87.17	10.00	25.65	24.99	-2.5	23.51	23.13	-1.6	15.76	15.82	-10.3	0.673
Average		.	87.03	88.50	10.5	25.63	25.56	-0.2	23.49	23.29	-0.9	15.75	16.14	-12.1	0.661
5/19/15	1	10.16	66.59	67.23	+0.5	19.70	19.85	10.7	18.05	18.19	10.7	12.10	12.52	-13.1	0.666
	2	10.11	66.57	66.21	-0.5	19.60	19.35	-1.27	17.97	17.76	-1.2	12.04	12.99	-12.0	0.667
	3	10.20	65.23	66.72	12.2	19.21	19.51	11.72	17.21	18.08	15.0	11.80	12.12	-12.7	0.671
Average . . .		.	66.23	66.72	10.7	19.50	19.58	10.1	17.71	18.01	11.5	11.98	12.41	-12.7	0.669
Total .		.	925.69	930.11	10.51	272.61	271.22	-0.51	269.46	268.54	-0.30	167.18	172.58	-13.13	AV 0.666

\* In most of the tests the solution contained 90 % by weight of ethyl alcohol

TABLE 2—DATA OF—

Subject, Date, Weight, Surface Area Linear Formula	Period	End of Period Time	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine $\lambda$ per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
John L 3/26/14 70.94 Kg	Prelim	11 20							
	1	12 20	21 12	19 51	0.70	23 77	0.363	64 65	66 00
	2	1 20	21 37	19 62	0.70	24 56	0.363	65 10	68 26
	3	2 20	21 07	19 97	0.78	24 01	0.363	65 85 <u>195 20</u>	66 72
John L 4/3/14 70.90 kg	Prelim	12 05							
	1	1 05	20 36	18 33	0.81	22 00	0.347	61 08	61 79
	2	2 05	19 04	18 47	0.70	23 66	0.347	61 19 <u>122 27</u>	63 45
Albert G 12/21/14 66.03 Kg 1.67 Sq M	Prelim	11 13							
	1	12 13	24 32	20 68	0.86	31 28	0.60	69 31	75 76
	2	1 13	25 07	20 96	0.90	31 59	0.60	71 08	78 38
	3	2 13	24 31	21 22	0.83	31 86	0.60	70 73 <u>211 12</u>	78 17
Albert G 12/23/14 63.03 Kg 1.63 Sq M	Prelim	11 09							
	1	12 09	24 73	20 49	0.88	23 81	0.636	68 89	62 75
	2	1 09	23 44	20 22	0.84	26 68	0.636	67 53	68 59
	3	2 09	26 11	23 15	0.82	28 22	0.636	77 07 <u>213 40</u>	69 69
Albert G 12/28/14 65.35 Kg 1.66 Sq M	Prelim	11 05							
	1	12 35	34 28	28 06	0.86	39 12	0.731	97 54	112 03
	2	1 05	35 80	29 23	0.89	39 24	0.731	99 06 <u>196 60</u>	107 08
Albert G 1/8/15 66.33 Kg 1.67 Sq M	Prelim	11 21							
	1	12 21	22 43	19 88	0.82	27 86	0.661*	66 09	68 10
	2	1 21	25 06	20 38	0.89	29 56	0.518*	69 16	72 48
	3	2 21	24 02	22 81	0.70	30 70	0.518	75 51 <u>210 76</u>	71 82
Albert G 1/9/15 65.85 Kg 1.67 Sq M	Prelim	11 13							
	1	12 13	25 35	21 50	0.86	33 84		72 89	75 78
	2	1 13	23 62	19 07	0.90	32 76		65 32 <u>138 21</u>	76 38
R H S 4/19/15 64.86 Kg 1.83 Sq M	Prelim	11 40							
	1	12 40	23 21	19 95	0.85	26 28	0.478	66 98	79 97
	2	1 40	23 79	20 87	0.83	26 25	0.478	69 82 <u>136 80</u>	77 61

\* Calculations for first period were based on a mean of these two figures

## —CALORIMETER EXPERIMENTS

[illegible]



TABLE 2—

Subject, Date, Weight, Surface Area Linear Formula	Period	End of Period Time	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	per Hour, Urine N Gm	Calo rimetry, Indirect Cal	Elimi nated, Heat Cal
R H S 1/21/15 63.35 Kg 1.78 Sq M	Prelim	11 22							
	1	12 22	21.75	18.69	0.81	24.82	0.397	65.76	76.49
	2	1 22	21.91	18.81	0.85	25.17	0.393	58.54	76.96
								124.30	
E F D B 5/6/15 71.61 Kg 1.91 Sq M	Prelim	11 17							
	1	12 17	23.43	21.39	0.80	31.59	0.528	70.75	70.84
	2	1 17	23.69	22.04	0.78	32.82	0.528	72.76	73.96
								143.53	
E F D B 5/7/15 74.20 Kg 1.90 Sq M	Prelim	11 18							
	1	12 18	23.12	20.51	0.82	33.52	0.593	68.22	76.92
	2	1 18	23.15	20.73	0.82	31.68	0.593	68.96	75.07
								137.18	
William A 1/25/15 63.44 Kg 1.80 Sq M	Prelim	11 13							
	1	12 13	25.32	20.31	0.91	34.45	0.382	69.44	72.53
	2	1 13	24.08	20.86	0.84	32.15	0.382	70.14	73.06
	3	2 13	24.45	22.02	0.81	31.11	0.382	73.44	73.48
								213.02	
William A 1/27/15 63.00 Kg 1.74 Sq M	Prelim	10 40							
	1	11 40	24.37	21.08	0.84	32.50	0.390	70.86	73.83
	2	12 40	25.01	22.17	0.82	32.87	0.390	74.09	75.33
	3	1 40	24.75	23.05	0.78	33.53	0.390	76.88	78.06
								221.83	
Theodore S 1/28/14 59.52 Kg	Prelim	11 10							
	1	12 10	23.13	20.30	0.83	39.03	0.454	67.86	77.28
	2	1 10	23.98	21.43	0.81	38.26	0.454	71.40	76.66
Theodore S 1/30/14 59.44 Kg	Prelim	11 15							
	1	12 15	21.66	18.76	0.84	36.00	0.385	62.97	73.11
	2	1 15	22.80	20.18	0.82	37.75	0.385	67.48	73.83
Theodore S 2/5/14 60.28 Kg	Prelim	11 46							
	1	1 16	31.63	31.59	0.80	50.61	0.538	105.10	118.65
	2	2 16	22.82	20.53	0.81	32.00	0.538	68.47	72.40
Theodore S 2/9/14 61.15 Kg	Prelim	11 50							
	1	12 50	21.11	18.41	0.83	21.14	0.394	61.66	56.93
	2	1 50	22.34	19.11	0.85	22.55	0.394	64.30	60.88
Theodore S 2/13/14 61.99 Kg	Prelim	11 10							
	1	12 10	24.54	20.49	0.87	26.73	0.391	69.38	70.40
	2	1 10	24.35	21.15	0.84	33.09	0.391	71.02	75.79

—(Continued)

Direct Calo rimetry (Rectal Temp ), Cal	Rectal Temp , °C	Average Pulse	Work Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbo-hyd	Per Kg	Per Sq M (Meeh)	
	37 00									In steamer chair
67 20	36 83	62	1 0	0 83	16	49	36	1 04	33 60	Almost motionless
78 30	36 86	57	6 0	0 86	18	39	43	0 92	29 91	Almost motionless
145 50										
	36 99									Basal, flat in bed
69 89	36 98	57	10 0	0 79	20	57	23	0 95	32 40	Very quiet
75 52	37 01	57	7 0	0 78	19	63	18	0 98	33 32	Very quiet
145 41										
	36 92									In steamer chair
67 38	36 76	57	9 0	0 83	23	45	33	0 92	32 12	Quiet
78 32	36 83	55	12 0	0 83	23	45	33	0 93	32 47	Quiet
145 70										
	36 96									Cardiac patient, flat in bed
62 29	36 77	62	20 0	0 93	15	20	65	1 10	35 47	Restless
69 48	36 71	60	11 0	0 85	14	68	18	1 10	35 82	Fairly quiet
70 55	36 66	62	10 0	0 81	14	62	24	1 16	37 51	Quiet
202 32										
										In steamer chair
66 72	36 76	66	10 0	0 85	15	44	42	1 13	36 36	Quiet
72 33	36 71	66	11 0	0 82	14	53	33	1 18	38 01	Quiet
73 06	36 62		21 0	0 78	14	65	22	1 21	39 19	Fairly quiet
212 11										
	37 14									Cardiac patient, flat on back
89 92	36 94	49	21 0	0 84	18	46	36	1 14	36 14	Restless
71 30	36 93	50	23 0	0 82	17	52	31	1 20	38 03	Restless
	37 10									Propped up in bed at angle of about 30 deg
70 46	37 05	53	1 9	0 85	16	44	40	1 06	33 58	
75 61	37 13	52	0 9	0 83	15	51	34	1 14	35 99	
	37 03									Flat on back, quiet both periods Pain in hand at 12 43 Periods 1½ Hrs
86 70	36 87	50	10 0	0 80	14	60	26	1 16	37 09	
72 40	36 94	47	0 6	0 81	14	56	30	1 14	36 26	
	37 06									Propped up in bed at angle of 50 deg Quiet both periods
64 71	36 83	49	6 7	0 84	17	45	38	1 01	32 28	
67 15	36 86	46	3 7	0 86	16	40	44	1 05	33 67	
	37 01									Flat on back
66 94	36 95	54	3 5	0 88	15	34	51	1 12	35 99	Quiet
75 32	36 95	55	5 5	0 84	15	45	40	1 15	36 84	Quiet

is accustomed to take moderate exercise and his general health is fair. This last year he has been doing much night work, has taken no exercise, and has lost about 5 pounds in weight. He is very tall, 184.2 cm and very thin, but not emaciated. His measurements and surface area are given in detail in Paper 9 of this series. His heart and lungs, etc., are normal.

April 19, 1915, he was in the calorimeter flat in bed for two hours to determine the basal metabolism, and two days later was in the steamer chair for a similar period. On both days he was awake but almost motionless.

E. F. D. B., man, 33 years old, a normal control, whose history is given in Paper 4<sup>10</sup> of this series. May 6, 1915, he was in the calorimeter flat in bed. Except for a small cup of black coffee without sugar, he had taken no food since 7.30 p. m. The steamer chair experiment, owing to a sudden change in plans, had to be made the next day. Unfortunately the subject had eaten a Welsh rarebit at 11 p. m., so it is possible that there was a slight specific dynamic action increasing the metabolism. He was quiet in both experiments.

#### CARDIAC PATIENTS

Theodore S., 32 years old, coachman, born in Sweden. Admitted Jan. 17, 1914, discharged February 22. Diagnosis, mitral stenosis, cardiac hypertrophy and dilatation auricular fibrillation.

*History*—Pneumonia when 6 years old, no rheumatism. Four or five years prior to admission the patient began to have shortness of breath on exertion. Three years previous to admission this compelled him to look for an easy job, but he was able to carry trunks upstairs until eight months prior to admission. For the previous two weeks the dyspnea had confined him to bed.

*Physical Examination*—Of medium build, 169 cm tall, well nourished and fairly muscular. He is slightly dyspneic, the lips are a deep red color, with a slight purplish tint. He has an occasional cough. The apex is in the fifth costal interspace 12 cm from the midline, the left limit of dullness 14.5 cm from midline, the right limit in the fourth space 4 cm from midsternum. The action is slow and very irregular in force and frequency. Phlebograms show auricular fibrillation. At the apex is heard the presystolic murmur to which Mackenzie and Lewis have recently called attention. The first sound is sharp and short, the second sound faint, followed immediately by a loud, rough rumbling murmur which diminishes during diastole, lasting through the short diastoles but followed by a period of silence in the long pauses. The pulse is small, the arteries palpable. There are a few subcrepitant râles at the bases of the lungs. The Wassermann reaction is negative. By January 26 all dyspnea had disappeared and there was not the slightest trace of orthopnea. He was able to sit in a chair without fatigue. There was no edema.

*Experiments*—January 28, basal experiment flat in bed. The patient was anxious to cooperate but he was of timid nature and during this first observation was a little anxious. His skin was cold and clammy at the start and he sweated profusely while in the calorimeter. January 30 he was propped up on the calorimeter bed at an angle of about 30 degrees. He was quieter than before. February 5 he was in the calorimeter flat in bed. Just as the first period was being ended he had a slight pain in his hand which caused him to sweat. This suddenly expanded the air in the box and raised the work adder 5 cm. The first period was prolonged one-half hour, by which time things had come into equilibrium. February 9 he was propped up with the back rest at an angle of about 50 degrees and made very comfortable with pillows at his back and under his knees. February 13 a third experiment with the patient flat in bed was made. He was comfortable and quiet but apparently began to sweat a little when signalled to lie quiet at the end of each period.

February 16 the systolic blood pressure was 145 mm lying down and 142 mm when sitting up at an angle of about 45 degrees. February 22 he was discharged in good condition and was able to walk up two flights of stairs slowly.

without dyspnea March 4 he was readmitted with a sharp attack of broncho-pneumonia from which he recovered, leaving the hospital on the 27th of that month

William A, 24 years old, laborer Admitted to the hospital Dec 28, 1914, discharged Jan 30, 1915 Diagnosis, aortic insufficiency, cardiac hypertrophy and dilatation History Has had measles, pneumonia, rheumatism and urethritis and has had frequent attacks of tonsillitis December 25 he had a sudden sharp pain in the side The following night he was very orthopneic and had a great deal of palpitation He complains also of weakness and cough

TABLE 3—SUMMARY OF CALORIMETER EXPERIMENTS ON BODY POSTURE

Subjects	Age, Years	Weight, Kg	Average Pulse	R Q	Average Calories per Hour		Posture
					Indirect Calorimetry	Direct Calorimetry	
Normals							
John L 3/26/14	44	70.94	58	0.78	65.20	61.10	Lying*
4/ 3/14		70.90	61	0.80	61.14	58.89	Sitting up
Albert G 12/21/14	24	66.03	54	0.86	70.37	71.68	Lying
12/23/14		63.03	54	0.85	71.16	64.37	Sitting up
12/28/14		65.35	53	0.88	98.30	106.80	Lying
1/ 8/15		66.33	56	0.84	70.25	69.82	Lying
1/ 9/15		65.85	61	0.88	69.10	70.28	Sitting up
R H S 4/19/15	21	64.36	60	0.84	68.40	72.03	Lying
4/21/15		63.35	59	0.84	62.15	72.75	Sitting up
E F D B 5/ 6/15	33	74.64	57	0.79	71.77	72.71	Lying
5/ 7/15		74.20	56	0.82	68.59	72.85	Sitting up
Cardiacs							
William A 1/21/15	24	63.44	61	0.85	71.01	67.44	Lying
1/27/15		63.00	66	0.81	73.78	70.70	Sitting up
Theodore S 1/28/14	32	59.52	50	6.82	69.63	80.26	Lying
1/30/14		59.44	53	0.83	65.23	73.04	Sitting up
2/ 5/14		60.28	49	0.80	86.79	76.01	Lying
2/ 9/14		61.15	48	0.84	62.98	65.93	Sitting up
2/13/14		61.99	55	0.85	70.20	71.13	Lying

\* Basal—flat in bed

*Physical Examination*—Tall (180 cm), well developed and well nourished, dyspneic and orthopneic, color pale

Tonsils swollen and congested Apex impulse diffuse, left border 13 cm right border 4 cm from midline There is a waterfall diminuendo diastolic murmur and a presystolic roughness considered to be a Flint murmur The pulse is Corrigan in type

The temperature, which has been slightly elevated, dropped to normal and the dyspnea and orthopnea disappeared A blowing systolic murmur became

audible in the aortic region By January 26 he was able to sit all day in a chair without fatigue

January 25 he was in the calorimeter flat on his back for three hours, and two days later was in the steamer chair for a similar period

#### METHODS OF EXPERIMENTS

The calorimeter and the experimental procedure have been described in Papers 1 to 4 of this series All the experiments were made in the morning without food, except in a few instances when a small cup of black coffee without sugar was used When the subjects were flat in bed they were allowed a pillow under the head, and if they desired it one under the knees

#### DISCUSSION OF RESULTS

Each experiment in the sitting posture is controlled by one or more observations on the same individual lying flat in bed, and we might therefore compare the average calories per hour produced under the

TABLE 4—SUMMARY OF RESULTS

Name	Average Pulse		Average Metabolism, Cal per Sq. M. per Hour, Meeh		Per Cent Difference in Semireclining
	Lying	Semireclining	Lying	Semireclining	
Normal Controls					
John L.	58	61	30.90	28.00	-6.1
Albert G.	54	58	34.29	31.71	-7.2*
R. H. S.	60	59	34.60	31.75	-8.2
E. T. D. B.	57	56	32.85	32.20	-1.7
Cardiac Cases					
Theodore S.	51	51	36.78	33.80	-7.7
William A.	61	66	36.27	37.55	+4.4
Average					-3.0

\* Omitting experiment of December 28, averages are metabolism, lying equals 35.01, per cent difference equals -1.0

two conditions The standard procedure in this laboratory, however, has been to compare the results in terms of calories per square meter of surface area per hour This latter method will be adhered to, since these experiments will be discussed from other points of view in the following papers It makes little difference which method is used, as the surface area scarcely changed at all between experiments

The results are summarized in Tables 3 and 4 It will be seen that the metabolism averaged 3 per cent lower in the semireclining than in the lying posture Of the four normal subjects, three showed this lower metabolism very clearly In one, Albert G., the average figure for the flat experiments is 12 per cent lower, but if the abnormally low result in the experiment of December 28, when he dozed, be

excluded, the balance will be 10 per cent on the other side of the line. It is unfortunate that it was not possible to have more cardiac patients in the series. The mitral case repeatedly showed a lower metabolism when propped up in bed, the aortic patient showed the opposite. Taken as a whole, the differences are so small that we may use the same figure for the average normal metabolism in both postures, and we need hardly change our normal base line when we discuss the experiments on patients who were so orthopneic that they had to use the steamer chair while in the calorimeter.

These results were somewhat surprising as the general opinion in the laboratory was that the heat production would be 5 to 10 per cent higher in the steamer chair. It must be remembered that previous investigators have used chairs in which the subjects sat upright or nearly upright, in some cases the head being unsupported. All the experimenters agreed that there was some muscular effort needed to maintain the posture and they ascribed to this the increase in heat production. In the orthopneic posture either with back rest or steamer chair as used in these calorimeter experiments, there was complete support of the body and head. No more muscular tension was needed than when the subjects were lying flat and the pillows were so arranged that the men could fall asleep without change in posture. It is quite possible that the diminished pressure on the diaphragm lessened the work of breathing enough to account for the lower metabolism.

On steamers, in clubs, and in those parts of our country where laziness is a science, men assume a semireclining posture with the head, back and feet supported on any convenient object. Patients who are very dyspneic are obliged to sit up and they can sleep only in the semireclining posture. The slight diminution in energy requirement may be a factor in leading them to assume the orthopneic posture, but with many cardiac and nephritic patients this economy is more than offset by increased muscular activity.

#### SUMMARY AND CONCLUSIONS

The Sage calorimeter in the season of 1914-1915 was fully as accurate as in the previous years. Alcohol checks gave the following total errors: heat  $+0.51$  per cent, oxygen  $-0.51$  per cent, carbon dioxide  $-0.36$  per cent, water  $+3.13$  per cent. The respiratory quotient averaged 0.666 while the theoretical quotient was 0.6667.

Four normal men and two cardiac patients were studied in the calorimeter lying flat in bed and in the semireclining position propped up with a back rest, or else in a comfortable steamer chair. A total of twenty-one experiments showed that the metabolism averaged 3 per cent lower in the semireclining posture. One of the cardiacs, and pos-

sibly one of the normal controls, showed a slightly higher metabolism when propped up in bed

The difference between the results is so small that in the study of pathologic cases we can use the same figures for the average normal metabolism in both postures. In the majority of cases, however, the energy requirement is lower in the orthopneic position

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# CLINICAL CALORIMETRY

## TWELFTH PAPER

### THE METABOLISM OF BOYS 12 AND 13 YEARS OLD COMPARED WITH THE METABOLISM AT OTHER AGES\*

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In the period of development of boys, the years immediately preceding puberty are of especial interest. By this time the figure has lost most of its childish characteristics and the mind has reached a point of great intelligence. Although the individual has scarcely passed the half-way mark in the years of growth, and has only attained half his future weight, yet he resembles the adult much more than he resembles the infant. At this stage the sex glands have not yet begun the rapid development of puberty with its profound effect on the whole organism. Curiously enough there is a sudden increase in the rate of growth which takes place at this time. In fact, we may consider boys in the period of prepubescence as individuals of adult form but of small size, growing rapidly, and as yet scarcely influenced by the internal secretions of the sex glands. The study of their respiratory exchanges may throw light on many problems.

Recent developments in the science of metabolism have emphasized the necessity of using, for purposes of comparison, only those experiments in which the subjects were absolutely quiet. Since the assimilation of food increases the metabolism during four or five hours following a small meal, and five to ten hours after a large one, it is important to use only experiments in which this specific dynamic action is either slight or absent. The necessity for absolute quiet has long been recognized by Johansson and the Zuntz school, but has only been fully appreciated elsewhere for the last five years or so. The observations of Rubner<sup>1</sup> and Sonden and Tigerstedt<sup>2</sup> were made before this was understood, and the children were studied in large respiration chambers where they sat fairly quiet in chairs, eating from time to time, or else, as in the case of Rubner's boys, moving about the room at will. This

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\* From the Russell Sage Institute of Pathology, in Affiliation with the Second Medical Division of Bellevue Hospital

1 Rubner. *Beitrage zur Ernährung im Knabenalter*, Berlin, 1902

2 Sonden and Tigerstedt. *Untersuchungen uber die Respiration und den Gesamtstoffwechsel des Menschen*, *Skand Arch f Physiol*, 1895, vi, 1



amount of activity might increase the metabolism anywhere from 10 to 30 per cent above the resting value, and it is obvious that the results can be compared only with those obtained on other individuals who have shown exactly the same amount of muscular movement. It is for this reason that, while the careful work of the above mentioned observers is of great value in showing the changes during the different ages for a given amount of activity, it cannot be used in comparison with the experiments in which the subjects are quiet.

The classical study of Magnus-Levy and Falk<sup>3</sup> established the fact that the metabolism is high during childhood and low after the onset of old age. These observers studied twenty-five children, twelve old men and women and twenty-five of intermediate ages. They used the Zuntz-Geppert apparatus, making several short experiments on each subject in the morning before breakfast, the individual lying at complete rest on a couch. It so happened that they included no boys between the ages of 11 and 14 in their list.

The metabolism during infancy has been well studied by Howland,<sup>4</sup> Schlossmann and Murschhauser,<sup>5</sup> Benedict and Talbot,<sup>6</sup> Murlin and Hoobler,<sup>7</sup> Bailey and Murlin<sup>8</sup> and others,<sup>\*</sup> all of these observers paying especial attention to the question of muscular activity. On account of the difficulty of keeping infants quiet, Benedict and Talbot, and Murlin, Hoobler and Bailey were obliged to feed most of their subjects shortly before the experiment was started. It is quite possible that a lowering of metabolism during sleep may have counterbalanced the slight increase due to the milk ingestion.

All of the above investigators have thrown new light on the subject. It would too greatly extend the bounds of this article to discuss in detail the several excellencies contained in their work. Of special interest is the fact that the metabolism of babies in the first month of life is

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3 Magnus-Levy and Falk. *Der Lungengaswechsel des Menschen in verschiedenen Alterstufen*, *Arch f Anat u Physiol*, 1899, Suppl. 315.

4 Howland. *Der Chemismus und Energieumsatz bei schlafenden Kindern*, *Ztschr f physiol Chem*, 1911, lxxiv, 1.

5 Schlossman and Murschauser. For references see note 6.

6 Benedict and Talbot. *The Gaseous Metabolism of Infants*, Carnegie Institution of Washington, Pub. 201, 1914, *Studies in the Respiratory Exchange of Infants*, *Am Jour Dis Child*, 1914, viii, 1.

7 Murlin and Hoobler. *The Energy Metabolism of Ten Hospital Children*, *Am Jour Dis Child*, 1915, ix, 81.

8 Bailey and Murlin. *The Energy Requirement of the New-Born*, *Am Jour Obst*, 1915, lxxxi, 1.

\* Just as this article is going to press Dr Benedict has kindly called attention to the following reference: Olin. *Carbon Dioxid Production in Boys of from 10 to 18 Years of Age*, *Finska Läkarsällsk Handl Helsingfors*, 1915, lvi, 1434.

very low. This was apparently first discovered by Hasselbach,<sup>9</sup> and later independently by Murlin,<sup>7</sup> who first brought it to general attention. The same point was shown in Table 7 of Paper 4 of this series.

The metabolism of normal adults has been thoroughly studied in the last few years. Benedict, Emmes, Roth and Smith<sup>10</sup> have collected 157 subjects, some of them as young as 15 years, using chiefly the Benedict universal respiration apparatus. Palmer, Means and Gamble,<sup>11</sup> with the same instrument, have collected a considerable number of normal records and Means<sup>12</sup> has recently calculated his results according to measurements taken by the new surface area formula described in Paper 5<sup>13</sup> of this series. We have also at our command the normal controls of Paper 4<sup>14</sup> and those of Papers 11 and 13, studied in the Sage calorimeter.

All of the above mentioned work on adults was done with very quiet subjects twelve or more hours after the last meal, and the technic of the observers was almost exactly the same. The results of these experiments have been charted in the accompanying curves, together with the work of Magnus-Levy and Falk, of Howland, Benedict and Talbot, Murlin and Hoobler, and Bailey and Murlin for comparison with the new results obtained on the boys 12 and 13 years old. Many other careful workers have studied the normal metabolism, but it has seemed best to use only the above mentioned investigations.

#### METHOD OF EXPERIMENTS

The Sage calorimeter and the methods employed in this research have been fully described in the previous papers of the series entitled *Clinical Calorimetry*<sup>15</sup>. The surface area of the boys was determined according to the so-called "Linear Formula" described in Papers 5, 9 and 10. The calories derived from protein were calculated from speci-

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9 Hasselbach. Respirations—For søg Paa Nyfødte Dørn, Bibliot f Læger, 1904, 8 de Række 5th Bind, 219.

10 Benedict, Emmes, Roth and Smith. The Basal, Gaseous Metabolism of Normal Men and Women, *Jour Biol Chem*, 1914, xviii, 139. Benedict and Roth. The Metabolism of Vegetarians as Compared with the Metabolism of Non-Vegetarians of Like Weight and Height, *Ibid*, 1915, xx, 231. Benedict and Smith. The Metabolism of Athletes as Compared with Normal Individuals of Similar Height and Weight, *Ibid*, p 243. Benedict and Emmes. A Comparison of the Basal Metabolism of Normal Men and Women, *Ibid*, p 253. Benedict. Factors Affecting Basal Metabolism, *Ibid*, p 263.

11 Palmer, Means and Gamble. Basal Metabolism and Creatinin Elimination, *Jour Biol Chem*, 1914, xix, 239.

12 Means. Basal Metabolism and Body Surface, *Jour Biol Chem*, 1915, xxi, 263.

13 *Clinical Calorimetry*, Paper 5, *THE ARCHIVES INT MED*, 1915, xv, 868, 870.

14 *Clinical Calorimetry*, Paper 4, *THE ARCHIVES INT MED*, 1915, xv, 835.

15 Papers 1 to 8, *THE ARCHIVES INT MED*, 1915, xv, 793-945, Papers 9 to 17, *Ibid*, 1916, xvii, 855-1059.

TABLE 1—RESULTS OF CALORIMETER—

[illegible]

## —EXPERIMENTS ON BOYS

[illegible]

mens voided between the hours of 9 a m and 1 15 p m Twenty-four-hour specimens could not be secured

The subjects of the experiments here discussed were all healthy, normal boys between their twelfth and fourteenth birthdays Two of them, F R S and J D D B, were related to members of the calorimeter staff, the others were Boy Scouts from one of the suburbs A month or so before the research had been planned the writer had given the required physical examination to a group of sixteen Boy Scouts The scout master selected as subjects for the experiments the five who most needed to earn money for uniforms Harry B was chosen because he was a patrol leader and able to manage the other boys All the eight boys lived in the suburbs except J D D B, who was home on a vacation from boarding school They were all bright mentally and active physically, apparently being in constant motion when not studying or sleeping The urine was examined in all cases and found to be normal

In order to accustom the boys to the apparatus, they were brought to the calorimeter room a week or so before the experiment, sealed in the apparatus for a short time and trained in the simple routine This was omitted in the case of F R S, who had helped his father build parts of the machine and was thoroughly familiar with the work All of the boys considered the adventure as a lark and not one was apprehensive A small breakfast, consisting of an egg, a slice of toast and a glass of milk, was allowed them at 7 o'clock, because it seemed probable that boys of this age would be ravenous and irritable if sent in from the country in a fasting condition

The problem of keeping the youngsters quiet for three hours was hard to solve It seemed best to allow them to read for one of the hours in a small book with large print This proved satisfactory, the work involved in holding the book and turning the pages was very small During the rest of the time the boys were bored F R S and J D D B remained quiet for two hours, but the former was so restless in the third period that experiments of this length were not attempted again For the six Boy Scouts another expedient was tried All the boys were anxious to earn pocket money and all were liberally paid for the experiments A system of fines was instituted and the boys were told that one cent would be withheld for each centimeter that the work-adder tallied above 15 per hour This figure was arbitrarily selected since it represents the average activity of a quiet subject who turns over once or twice an hour and shifts his position a few times to make himself comfortable The boys took good care not to approach the danger mark After the fine system was started the 15 centimeter mark was exceeded in only one period, and the lads as a group were the quietest of subjects

TABLE 2—SUMMARY OF EXPERIMENTS ON BOYS

Name	Age		Weight, Kg	Height, Cm	Circum- ference of Thorax, Cm	Signs Ap- proach- ing Pub- erty	Surface Area, Sq Meters		Calories per Kg per Hr	Meeh's Formula		Linear Formula		Aver- age R Q	Aver- age Pulse
	Years	Mos					Meeh's For- mula	Linear For- mula		Calories per Sq Meter per Hr	Per Cent above Adult Aver, 34.7	Calories per Sq Meter per Hr	Per Cent above Adult Aver, 39.7		
J D D B	12	2	34.52	152.8	67.3	+	1.305	1.224	1.62	42.8	23	45.6	15	0.84	77
Leslie B	13	3	28.53	140.8	61.8	±	1.150	1.050	1.90	47.1	36	51.6	30	0.82	88
Raymond M	12	7	30.41	140.5	65.8	0	1.200	1.084	1.94	49.1	42	54.4	37	0.81	85
Reginald F	12	8	35.44	148.2	68.2	+	1.328	1.220	1.75	46.6	34	50.7	28	0.94	79
F R S	12	10	32.09	141.5	66.2	0	1.243	1.124	1.79	46.1	33	51.0	29	0.83	80
Arthur A	13	8	30.59	146.6	65.4	0	1.204	1.126	1.84	46.6	33	49.9	26	0.78	81
Harry B	13	10	36.57	146.0	71.4	++	1.357	1.232	1.60	43.0	24	47.4	19	0.86	88
Henry K	13	11	35.98	148.2	67.7	±	1.343	1.224	1.66	44.4	28	48.8	23	0.86	87
Average									1.76	45.7	32	49.9	26	0.84	83

The question may be raised as to whether or not the breakfast taken by the subjects between 7 and 7 30 a m increased the metabolism between the hours of 11 and 1 o'clock. The standard meal allowed consisted of 1 egg, 1 glass of milk and 1 slice of toast with butter. They were shown standard portions of these and copied them as closely as possible, except Arthur A, who took nothing but 1 egg. The meal contained approximately 17 gm of protein, 22 of fat and 30 of carbohydrate, with about enough calories to maintain a boy  $5\frac{1}{2}$  hours, if we allow an increase of 20 per cent over the basal metabolism, to cover the journey to the hospital. J D D B, who took his breakfast half an hour later than the others, had the lowest metabolism and Arthur A, who took the smallest breakfast, had almost the highest heat production. Mr H L Higgins of the Nutrition Laboratory in Boston, kindly made a series of observations on a young man who took this same breakfast and found that the metabolism returned to its fasting level  $3\frac{1}{2}$  hours after the meal. It may perhaps be said that the metabolism was increased by the ride of fifty minutes in the train, ten minutes in the street cars and the walk of five minutes. The boys all reached the hospital by ten minutes past 9, sat in a chair for three fourths of an hour, undressed and lay on the bed within the calorimeter at about 10 o'clock, the experiment beginning at 11, or three and one half to four hours after breakfast. It will be noted that there was no significant drop in pulse rate or metabolism in the second periods. It is exceedingly doubtful if the combined increase due to the previous exercise, the specific dynamic action of food and the quiet reading amounted to 5 per cent above the fasting level at absolute rest.

#### DESCRIPTION OF SUBJECTS

F R S, 12 years and 10 months old. He has been perfectly well except for one attack of abdominal pain in 1911, diagnosed as appendicitis.

*Physical Examination*—Short, muscular and unusually well built, no signs of approaching puberty, disposition very active.

This boy was the son of the laboratory technician, who built and still operates the calorimeter, and he was thoroughly at home in his surroundings, having in fact helped to make the bed on which he lay. He was the only boy placed in the calorimeter for an experiment without previously staying for a short period in the apparatus. On the morning of the observation he took the standard breakfast at 6 40 a m. While in the calorimeter he read quietly for the first hour. In the second hour he tried to sleep and was somewhat restless for part of the time. In the third hour he read for five minutes, and during the remainder of the time was so restless that this period has been excluded from the averages.

J D D B, aged 12 years, 2 months. In 1911 he had measles, about six months prior to the experiment he suffered from a number of furuncles in the outer ear, and two weeks before the experiment had a cold in the head which lasted four days.

*Physical Examination*—Very tall for his age, complexion dark, bones long and not heavy, very little subcutaneous fat, muscles sinewy, temperament rather

high-strung but under good control, genitalia just beginning to develop, there were a few pubic hairs, voice not yet affected

On the morning of the experiment he took the standard breakfast at 7 45 a m, and came to the hospital in the street cars, being the only boy who lived in the city. In the first hour he was almost motionless and slept for a short time, and in the second period he read quietly in a small book

Raymond M, aged 12 years, 7 months. He remembers that he had whooping cough as a baby and that he had measles two years previous to the experiment. He is short, stocky and muscular, but the thorax is rather narrow with a prominent sternum. His complexion is light and his disposition quiet. His physical examination is normal except that the right tonsil is moderately enlarged. He shows no signs of approaching puberty.

On the morning of the experiment he took the standard breakfast at 7 30 a m. During the first period he read very quietly and in the second period tried to sleep.

Reginald F, aged 12 years, 8 months. He remembers no illnesses except measles, he is tall, slim, of graceful build, his hair is brown, the pubic hair is just making its appearance and his voice suggests slight change, both mammary glands are palpable, measuring about 10 by 2 mm. The left gland is slightly tender.

Standard breakfast at 7 15 a m. In the first period he was very quiet, reading for twenty minutes. In the second period he slept for twenty minutes but was restless during the remainder of the time.

Harry B, aged 13 years, 10 months. Born in England, has been in this country eleven years, had measles in childhood and two weeks before the experiment was sick in bed a couple of days with stomachache. The day before he noticed a slight infection of his finger which pained him until it discharged a little pus. On the day of the experiment it did not hurt and he felt perfectly well.

*Physical Examination*—Of moderate height and stocky muscular build, with broad shoulders, complexion fair. The left forefinger is red and slightly swollen near the nail, but there is no redness up the arm and no tenderness or swelling of the axillary nodes. The genitalia are approaching the adult type in development and there is a scant growth of pubic hair, and the mammary glands are just palpable. The voice has not yet started to change.

He took the standard breakfast at 7 15 a m. During the first hour he was awake but very quiet, and in the second hour he was also quiet, reading for thirty minutes.

Henry K, aged 13 years 11 months. Does not remember any illnesses except measles. He is tall, fairly muscular and well built except for the chest, which is narrow, with a prominent sternum. The upper jaw is narrow with high arch and prominent incisor teeth. His complexion is fair, his disposition quiet. The only sign of approaching puberty is a scant growth of pubic hair.

He ate the standard breakfast at 7 a m. In the first hour of the experiment he was practically motionless and in the second hour was very quiet, reading for fifty minutes.

Arthur A, aged 13 years, 8 months. Thinks he had measles and mumps when 3 or 4 years of age, three years prior to the experiment he broke his femur in a coasting accident. There is now no shortening of the limb. He is of slight, sinewy build with well formed chest, but gives the impression of being somewhat undernourished, complexion fair, disposition rather nervous, no signs of approaching puberty.

The evening before the experiment he was taken, with the other Boy Scouts, to an exhibition drill and in the excitement took no supper except one bun at 5 p m. On the morning of the observation in the calorimeter he ate nothing but an egg at 7 a m. He was very quiet both hours, reading forty minutes in the second period.



Leslie B, brother of Harry B, aged 12 years, 3 months. In childhood he had measles and chickenpox. For the last few months he has had no appetite for breakfast and had suffered from stomachaches. He is of small frame, rather thin and undernourished but his color is good and his muscles strong. His complexion is fair and his disposition bashful and quiet. His teeth are in poor condition and his tonsils are enlarged. In the abdomen several masses of constipated feces are palpable. The only sign of approaching puberty is a scant growth of pubic hair.

On the morning of the experiment he took the standard breakfast at 7 a. m. In the first period he was quiet, reading for forty-five minutes. In the second period he was unusually quiet, sleeping about three-quarters of the time. He was perfectly well until he came out of the calorimeter. He then felt faint, but recovered quickly.

#### DISCUSSION OF RESULTS

The total heat production in the eight experiments as measured by the method of indirect calorimetry was 985.93 calories, by the method of direct calorimetry 986.33 calories, a difference of 0.04 per cent.

A summary of the results obtained on the boys will be found in Table 2. It will be noted that the metabolism averaged 32 per cent above the adult figure per unit of surface area according to Meeh's formula, or 25 per cent above according to linear figure. The true significance of these results can be appreciated only if we consider the variations in the intensity of metabolism from birth to old age. It is for this reason that the results on normal individuals have been grouped in Charts 1 to 3. The first (Chart 1) represents the metabolism from birth to the age of 24 calculated per *kilogram of body weight*. It will be noted in general that the heat production of the infants shows wide variations, but at a much higher level than that of the adults. A uniform decrease in the metabolism becomes evident after the sixth year, becoming less marked after the twentieth year. In Paper 4 of this series we have mentioned the disadvantages of using the body weight as a basis of comparison of individuals of different sizes. Small animals show per kilogram a caloric production so much greater than that of large animals that it is almost a waste of time to compare children and adults by using this standard. For clinical purposes, however, the body weight is a convenient guide.

Chart 2 shows the metabolism from birth to the age of 24 expressed in terms of calories per square meter of body surface as determined by Meeh's formula. Lines have been drawn showing as nearly as possible the averages for males and females. It will be seen that the metabolism is low at birth, increases rapidly during the first year, reaches its maximum in the almost unexplored period between the ages of 1 and 6, falls quite rapidly until the age of 20, then very slowly. During infancy there is no apparent difference between the sexes, but after the age of 6 the girls and women have a distinctly lower metabolism.

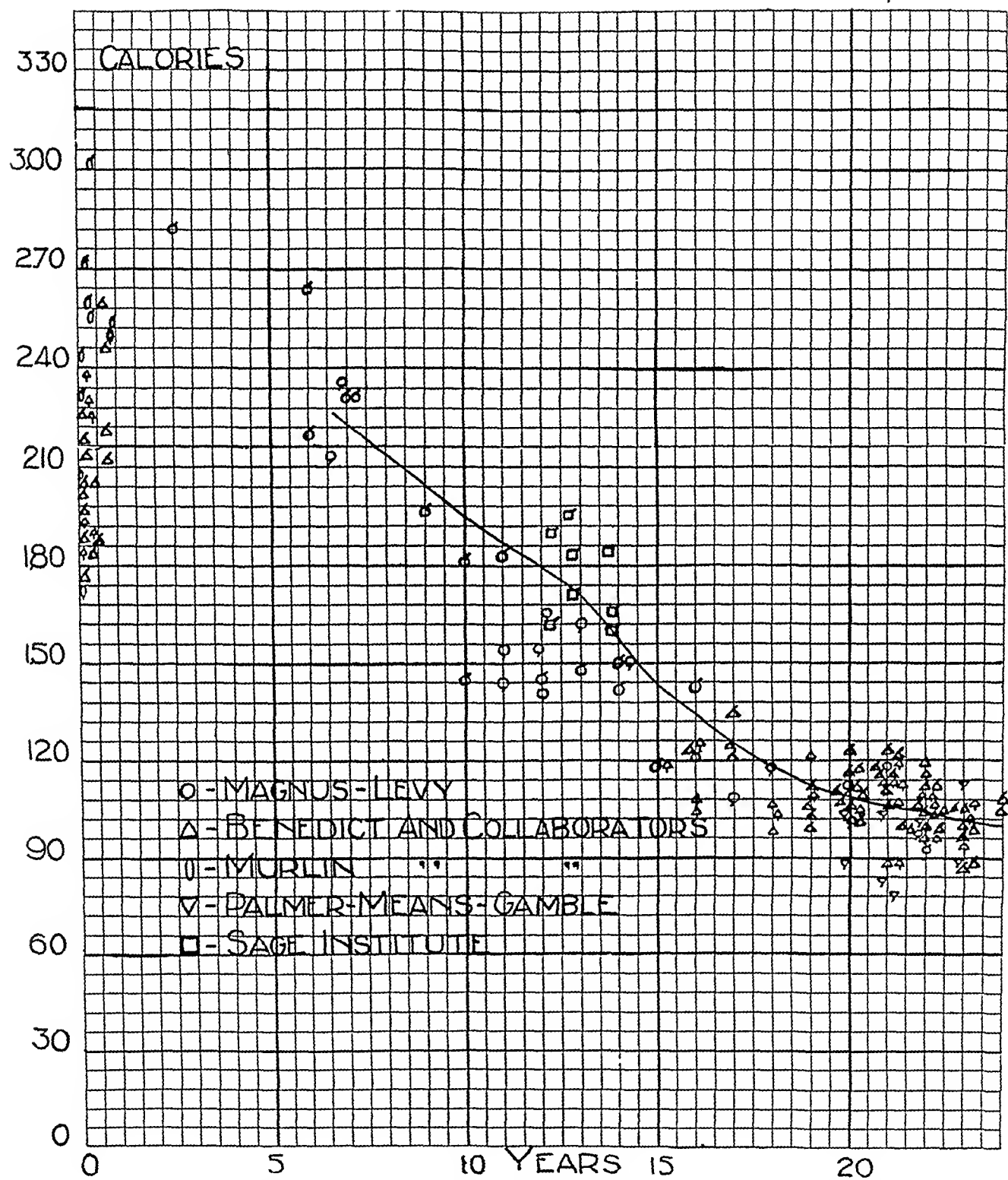
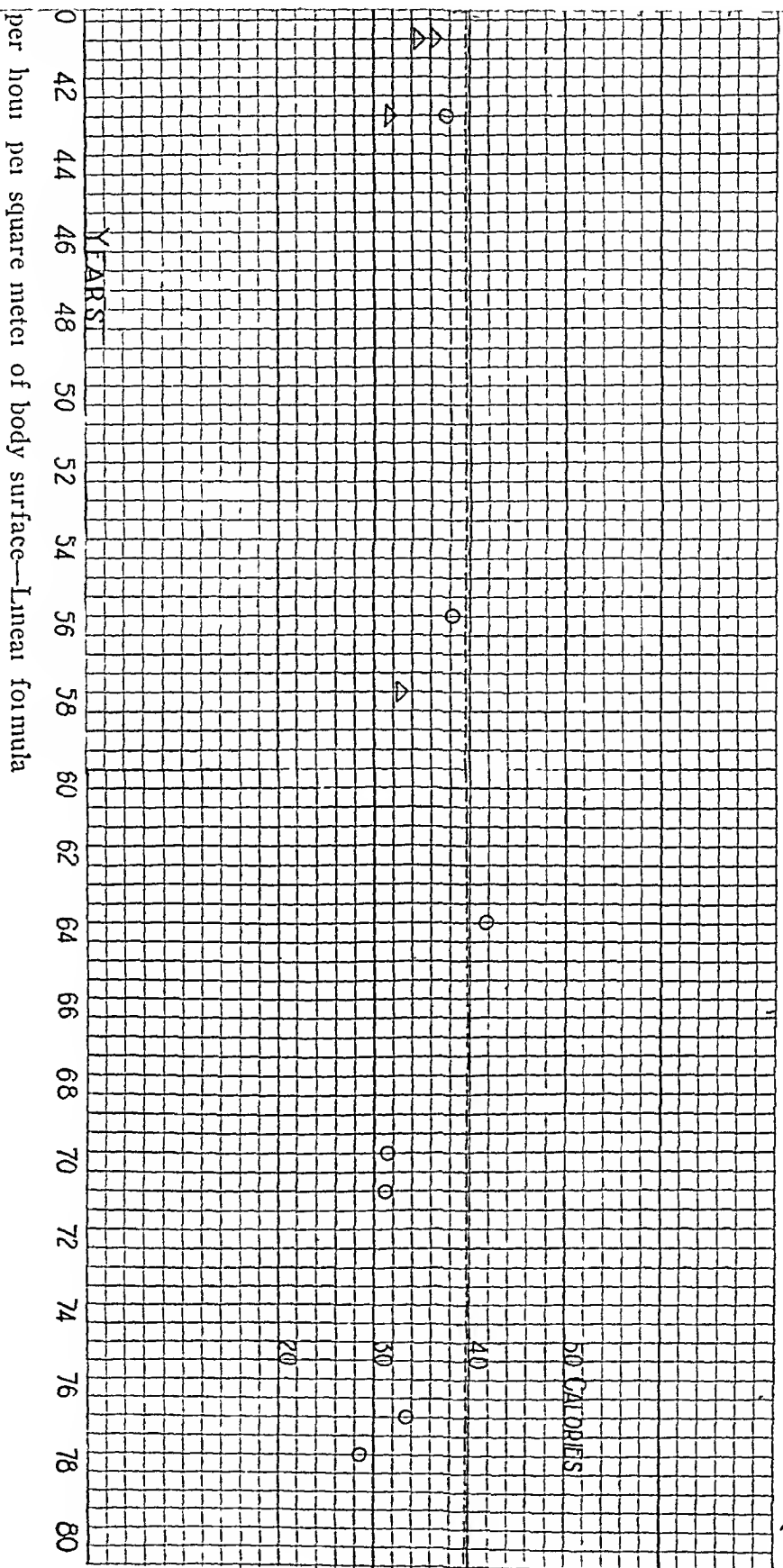


Chart 1—Variation of basal metabolism with age      Calories per hour per kilogram of body weight

In Papers 4 and 5 we have shown the reasons for preferring the calories per unit of surface area as a guide for the intensity of the metabolism, and have also shown the errors and limitations of Meeh's formula which has been the standard for so many years. The fact that the formula shows an average plus error of 16 per cent scarcely affects its value for purposes of comparison with subjects of usual build. On the other hand, the tendency of this error to be much smaller in the case of thin subjects and larger in the case of fat ones, is of considerable importance. New-born infants are relatively thin, older children relatively chubby until the age of 4 or 5, when they grow taller and thinner until puberty. Women tend to put on weight after 30 and men do so five or ten years later. If, therefore, we try to correct the curve for these errors in Meeh's formula we find that the peak in early childhood will be accentuated and the rest of the curve flattened out.

Chart 3 gives the results for males expressed in terms of calories per square meter of body surface as determined by the new so-called "Linear Formula." It will be seen that the metabolism of the adults is somewhat more uniform and that the boys average only 25 per cent above the adult level instead of 32 per cent as in the previous chart. This indicates a true increase of 25 per cent above the heat production which a group of normal adults would show if they were the same size as the boys. For purposes of comparison the metabolism of the infants has been recorded in terms of Lissauer's Formula<sup>23</sup>

When we consider the question of the metabolism in the first year or so of life we must remember that the infant differs greatly from the adult in the proportions of the body and the relative size of the various organs. A baby 5½ feet tall would be a short legged, long bodied monster with an enormous head. He would have a very large liver and a comparatively large thyroid gland. At birth the liver comprises 4.5 per cent of the body weight and during adult life less than 3 per cent. Since this is supposed to be a gland of high metabolic activity, one would naturally expect an increased heat production in an organism with a relatively large liver. Still more important in regulating metabolism is the thyroid gland, which is considered to be three times as large in the new-born as in the adult, although recent measurements by Pałski makes the figures somewhat smaller. Thyroid secretion has such a marked effect on development that it is quite possible that the gland is relatively more active in childhood. Some might even argue that the increased metabolism of this period is in itself evidence of a greater activity of the thyroid. Such a theory would be unwarranted unless supported by a greater number of facts than are now available. It should be remembered that the phenomena of growth are not so very different with invertebrates which have no thyroids.



# VARIATION OF BASAL METABOLISM WITH AGE

CAL PER HOUR PER SQ METER OF BODY SURFACE - LINEAR FORMULA

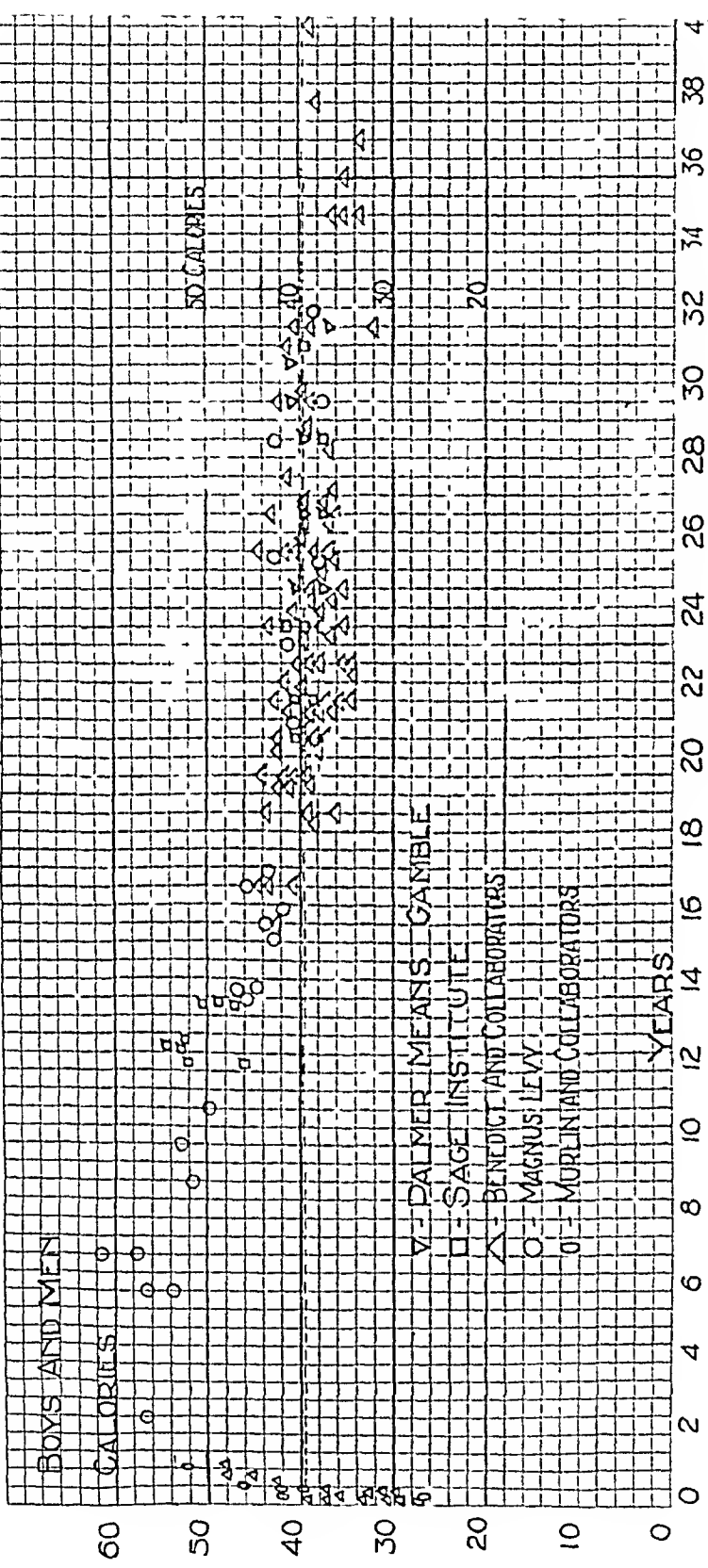


Chart 3—Variation of basal metabolism with age, Calories

The Sage calorimeter has recently been able to throw an interesting sidelight on the relationship of body form to metabolism. Two men who in youth had lost both legs in accidents, were studied in the respiration chamber and the surface area determined by formula and actual measurement. The one who was fat showed a metabolism only 4 per cent above the normal average, the one who was muscular was 2 or 3 per cent above. These men resembled infants in the relative proportion of body to extremities. This indicates that the law of surface area holds true under dissimilar physiological conditions such as are found in legless men. The high metabolism of infants is not therefore, due to the differences in body shape and body composition.

These factors are almost entirely ruled out in the case of the boys 12 and 13 years old. At this age the body has assumed almost the adult proportions and the liver and thyroid are not much larger in proportion to the body weight than in later life. The metabolism of these boys is very much higher than that of adults. It is rather a striking fact that the metabolism was distinctly higher in the boys who showed no signs of approaching puberty than in those who showed traces of pubic hair and increasing development of the genitalia. It is hoped that the same group of boys can be studied at intervals during pubescence. These boys can be compared with the case of infantilism studied by McCrudden and Lusk in the calorimeter of the Department of Physiology of the Cornell Medical College. This dwarf, who was 17 years old, and about the size of an average boy of 6 years, showed a metabolism of 23.3 calories per hour per square meter (Meeh), which was 7 per cent below the adult normal average.

The growth of children in length and weight is very rapid during the first two years of life and then decreases somewhat between the ages of 8 and 12. Following this is a period of increased growth, with relatively greater gain in stature than in weight. This begins in almost all the nations at the age of 12 or 13 in boys and reaches its height between the thirteenth and fifteenth years. The figures of Boas<sup>16</sup> and Burk<sup>17</sup> are well worth consulting, and Wiener's<sup>18</sup> measurements of three of his sons show this increase in the period of prepubescence very clearly. The curve of weight is somewhat different, since boys become relatively thinner as they grow tall and do not fill out again.

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16 Boas. *The Growth of Toronto Children*, Report U. S. Commr. Education, 1896-97, 11, 1541.

17 Burk. *Growth of Children in Height and Weight*, *Am. Jour. Psychol.*, 1898, 1x, 253.

18 Wiener. *Das Wachstum des menschlichen Körpers*, Karlsruhe, 1890.  
Chart reproduced in Burk's paper (note 17) and also in Hall's *Adolescence*, New York, 1904.

until puberty is well established. In the case of girls the period of increasing growth comes a year or two earlier.

In adult life the nearest approach to the growth of childhood is found in the period of convalescence from acute infectious diseases. The fact that the metabolism is increased at such times was demonstrated by Svenson, Rolly and others. Coleman and Du Bois<sup>19</sup> have shown that after typhoid the metabolism which falls to normal at the end of the fever, may rise to an average of 17 per cent above normal in the second and third weeks of convalescence. It is significant that the body which is repairing the losses of protein and fat during the fever should be maintaining its metabolism at a level which approaches that found in childhood. It is also significant that a second peak in the curve representing the heat production at different ages is found in the case of these boys just at the period of a renewed increase in the rate of growth. The evidence points toward a specific increase in the metabolism of the growing organism.

There is no apparent explanation for the fact that the metabolism was higher in the boys who showed no signs of approaching puberty than in the others. It is difficult to explain the low metabolism of newborn infants. It must be considered, however, that the unborn baby is essentially similar to an internal organ which is practically free from the play of external physical stimuli. Under such conditions the heat production must be on a different level from that in later life after a fuller development of the neuromuscular elements has been completed.

#### SUMMARY AND CONCLUSIONS

Eight normal boys, 12 or 13 years old, were studied in the respiration calorimeter four to six hours after a small breakfast. They were allowed to read for one of the two experimental hours, but were very quiet. The methods of direct and indirect calorimetry agreed within 0.04 per cent. Their heat production per unit of surface area was 32 per cent higher than the adult level according to Meeh's formula, or 25 per cent higher according to the more accurate "Linear Formula."

In studying the effect of growth on metabolism, interpretation of the results obtained on infants is complicated by the fact that babies differ greatly from adults in the proportions of the body and the relative size of the viscera, notably the liver and thyroid. Boys just before the onset of puberty have almost adult proportions. They are in the midst

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<sup>19</sup> Coleman and Du Bois. The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, *THE ARCHIVES INT. MED.*, 1914, xiv, 168, also *Clinical Calorimetry*, Paper 7, *ibid.*, 1915, xv, 887.

of a period of accelerated growth. The fact that the metabolism is high, points to a specific increase in the metabolism of the growing organism.

The writer wishes to thank those whose assistance made this research possible. The electrical measurements were made by Mr F G Soderstrom, the residual analyses and calculations by Dr A L Meyer and the calculations were checked by Miss Grace Sims. Urinalyses were made by Mr F C Gephart and Mr R H Stone.



# CLINICAL CALORIMETRY

## THIRTEENTH PAPER

### THE BASAL METABOLISM OF NORMAL ADULTS WITH SPECIAL REFERENCE TO SURFACE AREA\*

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NEW YORK

Since the writing of Paper 4<sup>1</sup> of this series an unusual amount of work has been published on the subject of the normal metabolism. It is now possible to calculate the normal baseline much more exactly than a year ago and it is therefore necessary to reconsider the whole question at this early date. The figures representing the average normal metabolism have been changed frequently since the study of the respiratory exchanges began and it may be said that the chief advance has depended on the fact that it has been possible to make the variation in the normal smaller and smaller each year. With the oldest type of large respiration chamber the range of heat production fluctuated enormously with the uncontrolled influences of muscular activity and the specific dynamic action of food. With the improved technique of Johansson and with the small apparatus of the Zuntz school these factors were eliminated, but errors due to changes in the calorific factors for O<sub>2</sub> and CO<sub>2</sub> remained. The normal variation was frequently quoted as from about 2.5 to 5.0 c.c. O<sub>2</sub> per kilogram and minute with a mean of about 3.5 c.c. Under these conditions a pathological departure from the average normal as great as 40 per cent might be obscured. In 1914 Coleman and Du Bois<sup>2</sup> gathered 48 controls from various sources including seven studied in the Sage calorimeter and gave the figure 34.2 calories per hour as the average heat production per square meter of body surface as determined by Meeh's formula. They pointed out that the normal variation was only plus or minus 10 per cent if the surface area were used as a standard. In Paper 4 of this series,<sup>1</sup> on the basis of a much larger number of controls, we selected the average

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1 Gephart and Du Bois. Clinical Calorimetry, Paper 4, *THE ARCHIVES INT. MED.*, 1915, xv, 835

2 Coleman and Du Bois. The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, *THE ARCHIVES INT. MED.*, 1914, xiv, 168

figure of 34.7. Since then Benedict, Emmes, Roth, and Smith<sup>3</sup> have published the details and have discussed their experiments which were only briefly reported at the time of our last publication. They found the metabolism of vegetarians to be practically the same as that of nonvegetarians, while the athletes average 7 per cent higher than the nonathletes used as controls. This is accounted for in part by the fact that the athletes were somewhat younger than the controls with whom they were compared. The average age of the fifteen athletes was 22 $\frac{1}{3}$  years and the average heat production 40.7 calories per square meter per hour as recalculated according to the height-weight chart. This is only 2.5 per cent higher than our standard for normal men. Benedict and his co-workers have pointed out the fact that the younger subjects show a higher metabolism and that the heat production is much lower when the subject is asleep at night than when he is awake in the day time. They have found the metabolism of women average about 6 per cent lower than that of men. The extremes of variation in the oxygen consumption of the same man over the course of months and years are shown in a very instructive table of thirty-five subjects. Eleven show a variation less than 10 per cent, eighteen show from 10 to 20 per cent and six a difference of 20 to 31 per cent, the average variation being 13.9 per cent. It must be remembered that this table shows the extremes, giving the percentage increase of the very highest period over the very lowest. The results in an early morning period when the subject was asleep may be contrasted with an afternoon period when he was awake and weary of experimentation. The "Universal" respiration apparatus with which these tests were made can be used only for periods of 10 to 20 minutes and with some people there may be a considerable amount of discomfort from the mouth or nose pieces. On the whole it is quite remarkable that the extremes of variation are not greater. It is to be hoped that the details of this table will be published so that we may estimate the frequency with which observations under similar conditions show results which differ materially from the average. Benedict also calls attention to the variation of the metabolism of different individuals according to body weight and surface area.

Palmer, Means and Gamble<sup>4</sup> have studied a considerable number of normal men and women and have found that the creatinin elimination bears a constant relationship to the basal heat production. Means<sup>5</sup> has

3 Benedict, Emmes, Roth and Smith *Jour Biol Chem*, 1914, xviii, 139; Benedict and Roth *The Metabolism of Vegetarians as Compared with the Metabolism of Non-Vegetarians of Like Weight and Height*, *ibid*, 1915, xx, 231; Benedict and Emmes *A Comparison of the Basal Metabolism of Normal Men and Women*, *ibid*, xx, p 253; Benedict and Smith *The Metabolism of Athletes as Compared with Normal Individuals of Similar Height and Weight*, *ibid*, xx, p 243; Benedict *Factors Affecting Basal Metabolism*, *ibid*, xx, p 265.

4 Palmer, Means and Gamble *The Basal Metabolism and Creatinin Elimination*, *Jour Biol Chem*, 1914, xix, 239.

5 Means *Basal Metabolism and Body Surface*, *ibid* 1915, xxi, 263.

calculated out the metabolism of these same subjects according to square meters of body surface as determined by Meeh's formula and by the new linear formula described in Paper 5 of this series. The average figure for men according to Meeh's formula was 33.2 calories per hour, according to the "Linear Formula" 39.6. The averages for women were lower, Meeh's formula 29.9, "Linear Formula" 38.2. The greatest variation from the average was 12.3 per cent according to Meeh's formula and 7.9 per cent according to the linear, the mean variations were 4.8 per cent and 4 per cent, respectively. Means<sup>6</sup> has also shown that the apparent depression of metabolism in obesity in most cases was due to the large plus error in Meeh's formula, and that according to the linear formula his two very stout subjects came within normal limits.

In Papers 5 and 9 in this series attention has been called to the variable plus error in Meeh's formula, which averages about 15 per cent, and a formula based on linear measurements has been described. In Paper 10 a "Height-Weight" formula is given which makes it possible to determine the approximate surface area of subjects described in publications in which the height and weight are stated. Results expressed in terms of square meters of surface area are comparable if either the linear formula or "Height-Weight Formula" be used, but are about 15 per cent higher than if Meeh's formula be applied. This necessitates the use of two different sets of figures to represent the average metabolism of men between the ages of 20 and 50—39.7 calories per square meter per hour according to the linear formula, 34.7 calories according to Meeh's formula. In Paper 11 it is shown that the metabolism is slightly lower in the semireclining posture than flat in bed. In Paper 12 the increase in metabolism during the period of growth is discussed in detail.

#### METHODS AND SUBJECTS

The methods described in Paper 4 of this series were followed in the present work. Many of the subjects have been reported in previous papers.

Morris S., former typhoid patient, is reported in Paper 6 where the history and experimental data are given. At the date of the experiments here discussed he was in perfect health. Dec. 17, 1914, a basal determination was made and the next day between 8.40 and 9.20 a. m. he ate the protein meal, consisting of 110 gm. egg white, 21 gm. egg yolk, 600 c.c. fat-free milk, 150 gm. pot. cheese and 10 gm. lactose. This according to analysis of the cheese and milk contained 96 gm. nitrogen. He was quiet throughout the experiment and during the third hour slept for forty minutes. The metabolism was much lower during this hour and it should be excluded from the averages.

Albert G. Normal control whose history is given in Paper 12. Dec. 30, 1914, he was given 79 gm. olive oil at 10.15 a. m. During the first and second periods

<sup>6</sup> Means. Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, xxvii, 121.

he slept fourteen and ten minutes, respectively Jan 4, 1915, at 10 13 a m he was given 115 gm commercial glucose, the equivalent of 100 gm pure dextrose. He slept most of the first period. In the third period the CO<sub>2</sub> and O<sub>2</sub> measurements were lost. The experiment was repeated two days later.

A P C, normal control, male, 24 years old, 179.4 cm tall, medical student in good health.

Jan 21, 1915, after having been on a low nitrogen diet for several days a basal determination was made.

R H S history in Paper 12.

E F B D history in Papers 4 and 12.

Emma W, normal control. History in Paper 9. She was in unusually good health and was able to take violent exercise. Her menses were regular and not profuse. On examination of the heart there was a marked respiratory arrhythmia and also an occasional premature systole. Several electrocardiographic plates were taken but no abnormal beats photographed, although it was possible to see the typical large diphasic swing of the shadow several times. The first experiment was made May 13, which was the second day of the catamenia. To control this factor a second basal determination was made May 17, the third day after the flow had ceased. She was almost motionless both days while in the calorimeter.

#### AVERAGE BASAL METABOLISM OF MEN

In Paper 4 the results of respiration experiments on 96 men were considered. To this group may be added the nine men of Palmer, Means and Gamble and the four men studied in the Sage calorimeter, Morris S, Albert G, R H S, and A F C. If we tabulate the results according to the surface area as determined by Meeh's formula there is no need to change the conclusions expressed in Paper 4. The average of the new cases is 33.6 calories per square meter per hour as opposed to the former figure of 34.7. It does not seem necessary to change the base line again. The greatest variation from the mean is 12.3 per cent as mentioned previously.

In Paper 4 of this series the results in five cases are given in terms of calories per square meter as determined by the new "Linear Formula." Adding the four new cases of this paper we have a total of nine normal men whose surface area has been accurately measured. The average basal metabolism is 39.7 calories per square meter per hour ("Linear Formula"). The extremes of variation from the average are +4 per cent and -6 per cent. John L, who was 44 years old, could not be found and measured. His results would probably have been further from the average. Means,<sup>5</sup> who measured his nine subjects by the same method, obtained an average figure of 39.6. Until we have a larger number of subjects measured in this manner the figure 39.7, given above, will be considered the standard with which all results are to be compared.

The results obtained by Benedict, Emmes, Roth and Smith may also be recalculated by means of the new "Height-Weight" chart. If we take the seventy-nine men between the ages of 20 and 50, who were of average body shape, and calculate the calories per square meter per

TABLE 1—DATA OF—

Subject, Date, Wt, ht, Surface Area, linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Albert G 12/30/14 64.91 Kg 1.637 Sq M	Prelim	11 15							
	1	12 15	23.94	21.20	0.821	39.51	0.418	70.78	74.34
	2	1 15	22.70	20.31	0.813	29.14	0.418	67.63	73.41
	3	2 15	25.40	21.21	0.871	29.47	0.520	71.51	73.73
	4	3 15	24.37	22.50	0.795	29.84	0.520	74.07	74.99
								251.19	
Albert G 1/4/15 65.64 Kg 1.665 Sq M	Prelim	11 12							
	1	12 13	20.97	23.79	0.916	31.69	0.415	81.52	81.57
	2	1 12	29.29	20.73	1.03	29.44	0.415	72.45	77.93
								153.98	
Albert G 1/6/15 66.16 Kg 1.671 Sq M	Prelim	11 11							
	1	12 11	32.55	22.59	1.05	39.35	0.509	79.19	77.67
	2	1 11	30.64	22.69	0.982	25.25	0.509	78.72	85.06
	3	2 11	29.03	21.73	0.972	33.69	0.509	75.20	77.63
	4	3 11	24.00	22.03	0.922	34.77	0.509	73.54	81.22
								306.65	
A T O 1/21/15 69.22 Kg 1.792 Sq M	Prelim	8 48							
	1	9 48	24.17	21.23	0.826	27.28	0.261	71.51	73.07
	2	10 48	23.10	20.33	0.830	27.49	0.261	68.44	72.90
								139.95	
Emma W 5/13/15 57.33 Kg 1.64 Sq M	Prelim	10 41							
	1	11 41	18.22	16.44	0.806	31.75	0.402	54.60	59.93
	2	12 41	18.41	16.18	0.827	29.11	0.402	53.94	56.21
								108.54	
Emma W 5/17/15 57.26 Kg 1.64 Sq M	Prelim	11 00							
	1	12 00	18.55	16.06	0.840	29.15	0.214	54.18	59.86
	2	1 00	18.86	16.77	0.818	27.93	0.214	56.21	52.26
								110.39	

hour, we obtain the figure 38.9. While this figure is slightly lower than ours, it must be remembered that it was obtained by means of the Benedict apparatus with periods only fifteen to twenty minutes long. For these periods the subjects can remain absolutely motionless, something impossible in calorimeter experiments two to four hours long. It seems preferable to use the average normal obtained in the calorimeter as a standard for pathological cases studied in the same apparatus.

## —CALORIMETER EXPERIMENTS

Direct Calo- rimetry (Rectal Temp), Cal	Rectal Temp, C	Aver- age Pulse	Work- Adder, Cm	Non- protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Pro- tein	Fat	Carbo- hyd	Per Kg	Per Sq M (Meeh)	
	37 00									Olive oil, 79 gm 10 15 a m
69 29	36 91	57	12	0 82	16	52	32	1 090	35 59	Asleep 10 min
79 53	37 03	61	7	0 81	16	54	30	1 042	34 00	Asleep 10 min
61 51	36 83	64	10	0 88	14	35	51	1 106	36 10	Awake
74 68	36 84	62	13	0 79	13	62	25	1 141	37 24	Awake
285 01										
	36 88									{ Commer glucose, 115 gm, water, 200 c c, 10 13 a m
94 63	37 12	65	7	0 94	15	17	68	1 242	40 73	Asleep
72 76	37 03	59	17	1 08	16	0	84	1 104	36 35	Awake
167 39										
	36 94									{ Com glu, 115 gm, lemon juice, 10 c c, water, 125 c c at 10 11 a m
74 57	36 89	66	11	1 11	17	0	83	1 197	39 32	Quiet
84 19	36 88	64	29	1 02	17	0	83	1 190	39 09	Quiet
75 70	36 85		30	1 01	18	0	82	1 137	37 34	Restless
72 69	36 70	57	15	0 83	18	47	35	1 112	36 51	Fairly quiet
307 15										
	36 89									Basal, low nitro- gen diet
61 25	36 69	68	30	0 83	10	52	38	1 033	34 45	Restless
60 55	36 48	74	20	0 84	10	70	20	0 989	32 97	Restless
121 80										
	37 04									Basal, 2d day of catamenia
54 38	36 93	60	2	0 81	20	52	28	0 952	29 80	Almost motion less
49 73	36 80	58	6	0 83	20	46	34	0 940	29 44	Almost motion less
104 11										
	36 91									Basal
46 26	36 82	57	4	0 85	10	46	44	0 946	29 61	Almost motion less
55 75	36 90	55	4	0 82	10	55	35	0 982	30 72	Almost motion less
102 01										

If we apply the "Height-Weight Formula" to the averages of the 68 women given by Benedict and Emmes<sup>7</sup> on page 256, we find that the approximate surface area for the average weight of 54.5 kg and average height of 162 cm is 1.57 sq meters. This would make their average heat production per hour 35.9 calories per sq meter, and if

<sup>7</sup> Benedict and Emmes: A Comparison of the Metabolism of Normal Men and Women Jour Biol Chem 1915, xx, 253

TABLE 2—SUMMARY OF RESULTS WITH NORMAL SUBJECTS  
(ALL MEN EXCEPT FRANK W.)

Name	Age, Years	Average Weight, Kg.	Height, Cm.	Sq. M. Surface Area		According to Meeh's Formula		According to Linear Formula	
				Meeh's Formula	Linear Formula or Measured	Cal per Sq. M. per Hour	Variation from Average per Cent	Cal per Sq. M. per Hour	Variation from Average per Cent
Morris S.	22	61.21	161.3	1.912	1.644	35.2	+1	41.2	+1
Albert G.	24	65.40	162.2	2.099	1.647	34.5	-1	41.2	+1
R. H. S.*	21½	61.6	184.2	1.777	1.800	31.6	-6	37.4	-6
L. I. D. B.	33	74.61	170.2	2.183	1.909	32.9	-6	37.7	-5
A. I. C.	21	67.22	170.4	2.076	1.792	33.7	-5	39.1	-2
Frank W.	26	77.32	161.8	1.831	1.642	29.9	-8	33.3	-10
Average for men						34.7		38.7	
Average for women						32.5		37.0	

\* Unusually quiet subjects

TABLE 3—THE BASAL METABOLISM DETERMINATION OF AVERAGE NORMAL FOR MEN BETWEEN AGES OF 20 AND 50\*

Name	Details Published in Paper	Average Calories per Sq. M. per Hour, Linear Formula
G. I.	4	40.7
E. F. D. B.	4 and 11	39.4†
R. H. H.	4	40.0
L. C. M.	4	40.5
F. C. G.	4	37.7
Morris S.	7	41.2
Albert G.	11 and 13	41.2
R. H. S.	11	37.4
A. F. C.	13	39.1
Average, Sage normal controls		39.7
Average, Means' normal controls		39.6
Average, Benedict's normal controls		38.9

\* Average calories per square meter per hour, according to the "Linear Formula" of men examined in Sage calorimeter. It has been impossible to find John L. and measure his surface area.

† Average of four basal experiments, Paper 4, first experiment Paper 11.

we add to the group the seven women studied by Means<sup>5</sup> the average for the whole would be 36.9 calories, a figure which may be adopted as the standard for normal women. This shows that the metabolism of women is about 7 per cent lower than that of men, a figure in agreement with the conclusions of Benedict and Emmes.

TABLE 4—A COMPARISON OF THE METABOLISM OF FAT AND THIN SUBJECTS TAKEN LARGELY FROM THE WORK OF BENEDICT, EMMES, ROTH AND SMITH

Name	Per Cent Deviation from Normal Average, 34.7 39.7		Calories per Kg per 24 Hours	Name	Per Cent Deviation from Normal Average, 32.3 36.9		Calories per Kg per 24 Hours
	Meeh's Formula	Height-Weight Formula			Meeh's Formula	Height-Weight Formula	
Fat Men— W S	— 12	+ 50	22.8	Fat Women— Dr M D	—11.2	— 10	18.9
O F M	— 8.6	— 0.5	21.3	O A	— 9.6	0.0	19.5
Prof C	—15.1	—12.0	19.9	H H	—17.0	— 7.0	18.0
F E M	— 6.9	— 4.0	22.7	H D	—10.3	+ 1.0	20.1
F A R	— 6.1	— 3.0	22.9	F M R*	— 6.8	+ 7.0	21.0
				D L*	—13.5	+ 1.0	19.7
				L F W*	—16.9	0.0	18.6
Average	— 7.6	— 4.0	21.9	Average	—12.2	0.0	19.4
Thin Men— R A C	+11.3	— 2.0	29.7	Thin Women— J T	+12.5	+ 2.0	31.7
B N C	+ 7.2	— 6.0	29.8	A A	+ 9.6	— 5.0	32.0
L E A	+ 7.6	— 2.0	29.5	E W	—12.2	+ 7.0	31.5
A F G	— 0.8	—10.0	27.0	A C	— 0.5	— 8.0	27.4
				J	— 2.1	— 7.0	26.9
				L B	— 6.7	—13.0	24.9
Average	+ 6.4	— 5.0	29.0	Average	+ 4.2	— 4.0	29.1

\* Means' subjects

#### A COMPARISON OF FAT AND THIN SUBJECTS

In Paper 4 of this series attention was called to the fact that in the case of fat individuals Meeh's formula would give a figure for the calories per square meter which would be very much too low. It might have been added that in the case of thin subjects the figure would be very much too high. The male subjects of Benedict and co-workers were plotted in our previous paper according to height and weight, and on account of the above mentioned errors six fat men and two thin ones were excluded from the averages. Now that it is possible to correct the error in Meeh's formula it has seemed advisable to compare



the metabolism of the fat and thin groups. A table compiled by the insurance companies showing the average weight of the male applicants between the ages of 25 and 29 years for different heights was taken as a standard. Those subjects whose weight departed more than 20 per cent from this standard were considered either fat or thin. H F was excluded on account of old age, two more thin men, L E A and A F G, were included in the new list. The fat and thin women were tabulated and three stout subjects of Means' added to the list. The results given in Table 4 are expressed in terms of variation from the averages for all normal controls, 39.7 calories per sq meter per hour "Linear Formula" for the men and 36.9 for the women. According to body weight the fat and thin groups show a difference of 41 per cent, according to Meeh's formula 15 per cent, according to the "Linear Formula" 3 per cent. This shows that Rubner's law that metabolism is proportional to surface area holds for fat and thin subjects and that we can safely use our new baseline for hospital patients whether they be fat or thin.

TABLE 5—BASAL METABOLISM OF NORMAL MEN AND WOMEN 40 TO 60 YEARS OLD, RECALCULATED IN TERMS OF SURFACE AREA BY THE "HEIGHT-WEIGHT" FORMULA

Subject	Investigators	Age, Years	Per Cent Deviation from Average Cal per Sq M per Hr (20-50 Yrs)
Men			Av 39.7
A L	B I R and S	40	-2.0
F G B	B I R and S	41	-8.0
Dr P R	B I R and S	41	-12.0
Dr S	B I R and S	43	-20.0
Prof Z	M L and F	43	-5.0
John L	G and D B	44	-12.0
G L	G and D B	47	+3.0
W	M L and F	56	-5.0
E J W	B I R and S	58	-17.0
Women			Av 36.9
B K	M L and F	40	+10.0
Mrs H D	B I R and S	42	+1.0
Dr M D	B I R and S	44	-1.0
Mrs S C	B I R and S	52	-12.0
Mrs E B	B I R and S	53	-1.0
Average, men and women		40 to 50	-4.3
Average, men and women		50 to 60	-11.3

## INFLUENCE OF AGE

In Table 5 are grouped the corrected results for the normal controls between 40 and 60 years of age. In Paper 4 the subjects between the ages of 20 and 50 were grouped together, but it is apparent that the average metabolism between the ages of 40 and 50 is 4.3 per cent lower than that of the whole group, while those between 50 and 60 are 11.3 per cent lower. It is necessary to use a lower figure for the baseline after the age of 50, and perhaps advisable to make the change at the age of 40.

## VARIATIONS IN METABOLISM

We have already spoken of the extremes in the oxygen consumption of the same individual during the course of months and years as reported by Benedict. Only a few of the subjects here reported have been studied over long enough periods to give much evidence on the question. The basal metabolism of E F D B was 35.91 calories per square meter per hour on March 13, 1913, the first time he was in the calorimeter, when he was somewhat restless. In May, 1913, it was 33.29, in March, 1914, 34.09, May, 1914, 32.97, May, 1915, 32.86. The extreme range was 9 per cent, and, excluding the first experiment, 3.7 per cent. Albert G. showed a variation of 6.4 per cent, the metabolism being unusually low on December 28, when he dozed during the two-hour experiment. In Paper 7 it will be noted that the curves representing the metabolism of the typhoid patients are very uniform.

## INFLUENCE OF FOOD

In a footnote to Paper 4 it was stated that Morris S. showed a rise of 6.5 per cent in metabolism two to six hours after a meal containing 9.6 gm. nitrogen. On recalculation the rise during the period turns out to be 7.4 per cent, and if we exclude the third period when he slept forty minutes, 11.9 per cent. This corresponds with the rise of 12 per cent found in the case of E F D B after a similar meal containing 10.5 gm. nitrogen. Albert G. on January 6, one to four hours after 11.5 gm. of commercial glucose, the equivalent of 100 gm. dextrose, showed an average metabolism 11 per cent higher than the basal determination two days later. This corresponds with the average of 9 per cent obtained with G L. and E F D B in the previous investigation. The one experiment on Albert G. one to five hours after 7.9 gm. olive oil showed little increase in metabolism. Fat exerts its chief specific dynamic action in the period immediately succeeding the hours studied. The glucose experiment on Albert G. January 4 was too short to be of value.

TABLE 6—WATER ELIMINATION THROUGH SKIN AND LUNGS NORMAL CONTROLS IN CALORIMETRIC BASAL METABOLISM EXPERIMENTS

Name and Date	Average H <sub>2</sub> O Gm per Hr	Average Calories per Hr Dir Cal	Per Cent Cal Lost through Vaporization	Per Cent Deviation from Mean 23.0%
G L 3/11/13	37.44*	80.88	27.7*	-14
E F D B 3/13/13	27.22	75.20	21.1	-12
5/17/13	32.90	71.44	26.4	+10
3/30/14	30.52	75.78	23.5	-2
5/18/14	28.06	68.60	22.9	± 0
5/ 6/15	32.21	72.71	25.9	-8
F O G 3/17/13	19.45	57.19	19.9	-17
4/22/13	27.44	60.72	26.4	+10
R H H 3/19/13	28.41	69.77	23.8	-0
Louis M 3/26/13	27.15	67.40	23.6	-1
John L 3/26/14	24.78	61.10	23.7	-1
I C M 5/ 4/14	27.80	70.21	23.1	-3
Albert G 12/21/14	31.58	71.68	25.7	+7
12/28/14	26.12	71.20	21.4	-10
1/ 8/15	29.37	69.82	24.6	+3
R H S 4/19/15	26.27	72.03	21.3	-11
Morris S 12/17/14	27.06*	70.33	22.5	-6
A F C 1/21/15	27.39	60.90	26.3	+10
Average 18 experiments on men	28.4		23.9	
Emma W 5/13/15	30.43	52.06	34.1	+42
5/17/15	28.54	51.01	32.6	+36

\* Much more warmly dressed than the other subjects

## WATER ELIMINATION

In Table 6 the water elimination from skin and lungs is given for the twenty basal experiments on normal adults. The first column expresses the averages for each experiment in grams per hour. Each gram vaporized at 23 C represents the loss of 0.584 calories. The second column gives the average calories produced per hour as measured by the method

of direct calorimetry The third represents the percentage of calories lost through vaporization It will be seen that normal men dressed in underwear and pajamas in a well ventilated box at 23 C give off between 19 and 32 gm of water per hour, dissipating in this manner between 20 and 27 per cent of the total heat produced The average figures are 28.4 gm per hour and 23.9 per cent of the calories Eighty-three per cent of the eighteen experiments come within 10 per cent of this last figure

There are many factors which influence the amounts of water given off by skin and lungs, the most important being the amount of water previously ingested, the amount of clothing, the temperature and humidity of the air and the rise or fall of body temperature The amounts eliminated in consecutive hours may vary greatly and even transient emotions may cause sweating The subject is too complicated to be treated in this short paper and is reserved for later discussion

TABLE 7—STANDARDS OF NORMAL METABOLISM AVERAGE CALORIES PER HOUR PER SQUARE METER OF BODY SURFACE

Subjects, Age in Years	According to Meeh's Formula	According to Linear and Height Weight Formulas
Boys, 12 to 13	45.7	49.9
Men, 20 to 50	34.7	39.7
Women, 20 to 50	32.3	36.9
Men, 50 to 60	30.8	35.2
Women, 50 to 60	28.7	32.7

#### SUMMARY AND CONCLUSION

The basal metabolism of four normal men and one woman has been determined and experiments have been made on the specific dynamic action of protein and glucose A study of the new controls, together with those reported in the literature since our last publication, supports the views previously expressed There is no reason to change the statement made in our previous paper, that if a given subject's basal metabolism is more than 10 per cent from the average, it may be regarded as abnormal, but cannot be proved abnormal unless the departure from the average is at least 15 per cent The average basal metabolism of normal men is 34.7 calories per square meter per hour as determined by Meeh's formula On account of the average plus error of about 15 per cent in Meeh's formula the average figure is 39.7 calories, or in round numbers 40 calories, when the more exact "Linear Formula" or the new "Height-Weight Formula" is used to determine surface area

The average metabolism of fat and thin subjects is the same according to surface area when the surface area is correctly measured. The metabolism of women averages 37.0 calories, or 6.8 per cent lower than that of men. A group of men and women between the ages of 40 and 50 gave figures 4.3 per cent below, and a group 50 to 60 years old 11.3 per cent below the average for the larger group between the ages of 20 and 50.

Under the atmospheric conditions of the calorimeter experiments the average water elimination by normal men through skin and lungs is 28.4 gm. an hour. About 24 per cent of the heat produced is dissipated in the vaporization of water.

The figures for the specific dynamic action of protein and glucose previously obtained are confirmed. A table of normal standards is given.

# CLINICAL CALORIMETRY

## FOURTEENTH PAPER

### METABOLISM IN EXOPHTHALMIC GOITER \*

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To those who are accustomed to think in terms of the energy requirement, exophthalmic goiter stands out *par excellence* as the disease of increased metabolism, and the increased metabolism stands out as the chief symptom of hyperthyroidism. The determination of the heat production seems to afford the best index of the severity and course of the disease. There is great need of some purely objective test in hyperthyroidism to indicate the effect of treatment, since psychotherapy can modify profoundly all subjective symptoms. At present the scientific status of the treatment of exophthalmic goiter is about at the point where we would be with diabetes if there were no laboratory tests for glucose and the acetone bodies.

No one of the simpler objective tests taken alone gives an accurate idea of the course of the disease, but when a number are taken together and added to the clinical impression of the observer, they afford a rough measure of the severity of the case. The rapidity of the heart action is perhaps the best guide, but the heart is often affected by other conditions, and damage to the heart may outlast the other symptoms. Rise in temperature is so irregular as to preclude its use as a reliable

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index. Changes in the size of the gland do not parallel the course of the disease. Changes in weight, warmth of skin and sweating are but consequences of the increase in heat production. Eye symptoms, tremor, nervous irritability, weakness, diarrhea are all too variable to be of reliance and are too difficult to measure accurately. The blood pressure is of some use as a guide, but it is affected by age and the condition of the cardiovascular system. The sugar tolerance depends on other ductless glands as well as the thyroid, and even in health has wide limits. The mononucleosis which has been considered characteristic by Kocher, Halsted and others is found in other diseases, and does not seem significant enough to be our main reliance.

In contrast to the above mentioned symptoms, an increased basal metabolism is found with great regularity in exophthalmic goiter, and in severe cases reaches a level found in no other condition. On the other hand, in cretinism and myxedema the metabolism is lower than in any other disease. The administration of thyroid extract, particularly in myxedema, raises the heat production. All other diseases in which metabolism is increased are easily distinguishable from exophthalmic goiter, and they never approach the extremes found in this condition. The basal metabolism is higher than normal in youth, in fever, in lymphatic leukemia and pernicious anemia, in severe cardiac disease and in some cases of severe diabetes and cancer. It is lower than normal in old age, in some wasting diseases and perhaps in some cases of obesity. Diseases of the ductless glands other than thyroid show in some cases an increase, in some a decrease, but these are comparatively small.

The theories of exophthalmic goiter at present are in a somewhat chaotic state. The suprarenals, thymus and most of the other ductless glands are thought by many to be involved, and the symptoms have lately been divided into sympatheticotonic and vagotonic groups. Even in regard to the thyroid itself some advance the theory of dysthyroidism in addition to or in place of hyperthyroidism. Such confusion is natural when we have few objective tests and many bizarre symptoms which can be ascribed at will to various ductless glands whose functions are obscure. It would seem as if we needed more laboratory work for those who hold no brief for any particular kind of therapy. Even the most extreme advocates of the new theories ascribe the chief rôle to an overactivity of the thyroid gland. For the purpose of simplicity in this paper one may consider the symptoms of exophthalmic goiter to be caused by too much thyroid secretion and allow the reader to select for himself those cases in which he believes other glands to be involved.

## PREVIOUS STUDIES OF THE RESPIRATORY EXCHANGES

The question of the metabolism in exophthalmic goiter has been reviewed by Magnus-Levy,<sup>1</sup> Hirsch,<sup>2</sup> and Falta,<sup>3</sup> Scholz<sup>4</sup> has given a large number of references on the subject of cretinism

Friedrich Muller,<sup>5</sup> in 1893, first pointed out the increase in metabolism in exophthalmic goiter by showing that a patient lost weight and nitrogenous substances on a diet that was more than sufficient to cover the needs of a normal person Magnus-Levy<sup>6</sup> two years later was the first to demonstrate the increase in the respiratory metabolism in hyperthyroidism and the decrease in myxedema Since then he has studied many cases of both diseases and has used the respiratory metabolism as an index of the effects of treatment, thus demonstrating the increase in heat production following the administration of thyroid extract He found that in myxedema the rise in heat production began in the first week of the administration of the extract and increased gradually till the fourth or fifth week The effect was most pronounced in severe cases, causing a rise of from 50 to 70 per cent In the mild cases the increase was slight, never going above 20 per cent, and in five of the nine normal controls there was no rise at all Stuve,<sup>7</sup> who worked with Magnus-Levy, found that thymus extract had no effect on the heat production Magnus-Levy and Stuve found the metabolism greatly increased in exophthalmic goiter, and their results, together with those of the others who have studied this subject, are recorded in Table 1 Thiele and Nehring,<sup>8</sup> and Anderson and Bergman<sup>9</sup> studied the influence of thyroid extract, the former finding an increase in the metabolism of obesity patients after its use and the latter no increase with two normal men

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1 Magnus-Levy Von Noorden's Handbuch der Pathologie des Stoffwechsels, Berlin, 1906

2 Hirsch Rahel Oppenheimer's Handbuch der Biochemie, iv, 2, 165

3 Falta Die Erkrankungen der Blutdrusen, Berlin, 1913

4 Scholz Klinische und Anatomische Untersuchungen über den Cretinismus, Berlin, 1906

5 Muller, Friedrich Beitrage zur Kenntniss der Basedowische Krankheit, Deutsch Arch f klin Med, 1893, li, 335

6 Magnus-Levy Gaswechsel bei Thyroidea, Berl klin Wchnschr, 1895, xxxii, 650, Untersuchungen zur Schilddrusenfrage, Ztschr f klin Med, 1897, xxxiii, 269, Ueber Myxoedem ibid 1904, liii, 201

7 Stuve Respiratorische Gaswechsel bei Schilddrusenfütterung Morbus Basedowii u sw, Fest Stadt Krankenh Frankfurt a M Mahlau 1896

8 Thiele and Nehring Untersuchungen des respiratorischen Gaswechsel unter dem Einflusse von Thyroideapreparaten und bei anaemischen Zustanden des menschen Ztschr f klin Med xxx 41

9 Anderson and Bergmann Einfluss der Schilddrusenfütterung auf den Stoffwechsel des gesunden Menschen Skand Arch f Physiol, 1898, viii, 326



TABLE 1—GOITER CASES IN THE LITERATURE ARRANGED—

Observer	Patient	Sex	Age Years	Duration of Disease Years	Clinical Classification
Hirschlauff	Louise B	♀		9	Very severe last ten days of life
Author	Case 6 (Anna K.)	♀	26	10	Severe
Author	Case 3 (James McL.)	♂	29	1 ( ) 1 1 ( )	Severe
Salomon	R H	♂	40	11	100% above average for women
Hirschlauff	Louise B	♀	21	9	Five months before death
Magnus Levy	Frl I B	♀	20		Severe acute
Salomon	Fall I	♂	27	5	
Magnus Levy	Frl K		26	26	Very severe, pregnant six months
Undeutsch	Frl	♀	24	1 1/2	"Zunächst Schwer"
Author	Case 1 (Max W.)	♂	40	14 1/2	Severe
Magnus Levy	Frl G	♂	25		Severe
Undeutsch	K	♀	2	1	(Mod. severe)
Magnus Levy	Frau Sehr	♀	42		Very severe
Pribram and Porges	Frl Tesch	♀	25	2	(Mod. severe)
Author	Case 2 (Edwin T.)	♂	20	1 1/2	Acute, mod. severe
Pribram and Porges	M S		25	1 1/2	(Acute, mod. severe?)
Salomon	M J	♀	25	1 1/2	(Mod. severe)
Magnus Levy	Frl I T	♀	22		Severe
Magnus Levy and Stüve	Frl R. B.	♀	26		Severe
Author	Case 4 (Dr. G. S. L.)	♂	52	3-4	Severe
Salomon	Fall II	♀	19	1 1/2	
					50% above average for women
Magnus Levy	Frl J	♂	20		Severe
Falta	J H		22		(Mild?)
Falta	R Fl	♀	34 1/2	3	(Severe?)
Author	Case 9 (Marlon B.)	♀	22	3	Mild, operated
Author	Case 8 (Sarah M.)	♀	29	3	Mild, operated
Magnus Levy	Frl Ung	♀	55		Severe
Author	Case 7 (Anna R.)	♀	29	5	Moderately severe
Author	Case 10 (Margaret L.)	♀	51	1	Atypical eardiae
Magnus Levy	M P.	♂	11 1/2		Small struma, otherwise normal
Magnus Levy	Frl O	♀	54		Simple goiter
Stüve and Magnus Levy	Frl G W	♀	24		Severe



TABLE 1—

Observer	Patient	Sex	Age Years	Duration of Disease Years	Clinical Classification
Magnus Levy	Trl M Kr	♀	26		Mild
Falsta	Ad K	♂	33	6	(Severe)
Landesdich	Wlt	♀	24	14	'Forme fruste'
Magnus Levy	Hr Bc	♂	40		Mild
Magnus Levy	Trl T W	♀	21		Severe
Magnus Levy	Fr B	♀	52		Half way between Kropf and forme fruste
Author	Case 5 (Peter N.)	♂	23	5	Atypical, operated Upper normal built for women
Magnus Levy	Hr R B	♂	20		Mild Average for normal men
Magnus Levy	Trl U	♀	55		Typical, mild
Author	Case 11 (Miss B. H.)	♀	31	1	Atypical, operated
Magnus Levy	Trl I D	♀	25		Simple goiter
Magnus Levy	Trl Seh M	♀	28		Mild
Magnus Levy	Trl M Kl	♀	17		Simple goiter Average for normal women
Magnus Levy	Trl Rh	♀	36		Half way between Kropf and forme fruste simple goiter

\* In this column, ♂ denotes male and ♀ female

Hirschlaff<sup>10</sup> made one of the most valuable contributions to the subject by studying in great detail over a long period a very severe case of hyperthyroidism which eventually came to necropsy. The oxygen consumption of this patient was about 77 per cent above normal, rising to 105 per cent above normal in the last week of life. Magnus-Levy considers that some of the high results on this patient were due to restlessness, but some were obtained while she was under the influence of morphin. This careful laboratory work on one patient is of more value to science than the clinical observation of a hundred patients. Jaquet and Svenson<sup>11</sup> found no constant rise in metabolism when they treated cases of obesity with thyroid extract. They also studied the specific dynamic action of food on these patients, and concluded that it was less than normal before treatment with thyroid

10 Hirschlaff, W. Zur Pathologie und Klinik der Morbus Basedowii, Ztschr f klin Med, 1899, LXXVI, 200

11 Jaquet and Svenson. Zur Kenntniss des Stoffwechsel fettsuchtigen Individuen, Ztschr f klin Med, 1900, LI, 375

—(Continued)

Calories per Sq M per Hr Meeh	Pulse Rate	Blood Pressure, Syst	Enlarge- ment of Heart to Left, Cm	En- large- ment of Thy- roid	Exoph- thal- mos	Von Graefe Sign	Mental irrita- bility	Tremor	Warmth of Skin	Ema- ciation	Remarks
39.7	80										
39.7	120-140	140	2	++	—	—	+	++	++	+	
37.7	100+	125	0	+	—	—	++	++	+	±	
37.0	78										
36.5	128										
35.7	96		±	!	—	—		±			
35.5	72-94		1	±	—	—	+	++	—	+	Four arteries ligated 1 yr ago
34.7											
34.7											
34.7	88-90										
34.6	72-96	112-120	0	—	±	—	++	+	—	+	Parathyroi- dect 2 mos ago
34.6	86										
34.1	80										
33.0											
32.3											
29.4	72-92		0	±	±	+		±			Hysterical temperament

extract but greater than normal after treatment. Salomon<sup>12</sup> considered the increase in metabolism to be the most important objective symptom of hyperthyroidism, and followed it during treatment with "Radogen" and the serum of a thyroidectomized horse. Neither of the remedies caused a fall in the metabolism. Steyrer<sup>13</sup> studied the effects of thyroid tablets on one exophthalmic goiter and one myxedema patient, using a Pettenkofer-Voit respiration chamber. Pribram and Porges,<sup>14</sup> working under Salomon, studied the "nuchtern" or basal metabolism from fifteen to seventeen hours after the last meal of diets containing various amounts of nitrogen. They found the heat production from 4 to 8 per cent higher the morning after a diet containing from 31 to 42

12 Salomon H. Gaswechseluntersuchungen bei Morbus Basedown und Akromegalie, Berl klin Wchnschr 1904 XLIV 635

13 Steyrer A. Ueber die Stoff und Energieumsatz bei Fieber, Myxoedem und Morbus Basedown Ztschr f exper Path u Therap 1907, iv 720

14 Pribram and Porges. Ueber den Einfluss verschiedenartiger Diatformen auf den Grundumsatz bei Morbus Basedown Wien klin Wchnschr, 1908, LVI 1584

gm of nitrogen than after mixed diets rich in carbohydrate. They do not consider that this differs from what would be found in normal persons after such excessive protein feeding, and believe that the basal metabolism is not much influenced by protein or meal abstinence. In one patient two treatments with the Roentgen ray did not cause any drop in the oxidative processes. More recently Undeutsch,<sup>15</sup> using the Rolly-Rosiewicz modification of the Benedict universal respiration apparatus, compared the rise in metabolism following the administration of various forms of protein to patients with exophthalmic goiter. He found that 40 gm of Menronat increased the metabolism more than 35 gm Rohorat and that both had greater action than 200 gm chopped beef. Two normal controls gave the same results. He concludes that animal protein has a lower specific dynamic action than vegetable. Undeutsch also made observations on three of his patients from one to two weeks after a partial thyroidectomy. One patient showed a drop of more than 10 per cent in the heat production, one a drop of 20 per cent and a third with "forme fruste" and colloid goiter only a slight reduction.

Von Bergman<sup>16</sup> studied several myxedema patients finding the metabolism moderately decreased. He observed a rise of 25 per cent in the heat production in an obesity patient after the administration of thyroid extract. Falta<sup>17</sup> reports respiration experiments on three of his exophthalmic goiter patients made by Dr. Bernstein. Means,<sup>17</sup> studying several obesity patients and making a large number of respiration experiments on one marked case, found a marked rise in metabolism after thyroid administration.

The literature on the treatment of exophthalmic goiter is too enormous to be reviewed in this paper, and only those remedial measures used on the patients here described will be discussed. A partial thyroidectomy has been and perhaps always will be the standard method of treatment. Recently many surgeons have been ligating one or more of the thyroid arteries under local anesthesia as a preliminary to the more radical operation or in place of it. Medical treatment gives slower results which are often very satisfactory. Mental and physical rest over long periods of time, combined with abundant food, almost invariably improves the patient's condition, and in many cases there is a tendency toward recovery without any treatment. Beebe and

15 Undeutsch, W. Experimentelle Gaswechseluntersuchungen bei Morbus Basedowii, Grundumsatz und Umsatz nach Aufnahme von animalischem und vegetabilischem Eiweiss, Inaug. Dessert, Leipzig, 1913.

16 Von Bergman. Der Stoff und Energieumsatz beim infantilem Myxoedem und beim Adipositas universalis mit einem Beitrage zur Schilddrusenwirkung. Ztschr. f. exper. Path. u. Therap., 1909, v, 646.

17 Means. Studies of the Basal Metabolism in Obesity and Pituitary Disease, Jour. Med. Research, 1915, xxxii (New Series, xxvii), 121.

Rogers,<sup>18</sup> and more recently Beebe<sup>19</sup> alone, have used a cytotoxic serum prepared by injecting sheep with an extract of human thyroid tissue. This serum has never come into general use. Some patients cannot take the serum on account of violent local and constitutional reactions and others who can take it show little improvement, as is the case with all other forms of treatment. Rogers<sup>20</sup> uses partial thyroidectomy in some cases, and serum in a few others, but places his chief reliance on ligation of two or more of the thyroid arteries as giving the best results in the long run. He has used thyroid extract in some cases for a few days after the ligation, and in other asthenic patients has given a thyroid preparation called "X Thyroidin," or thyroid "residue." Forchheimer<sup>21</sup> is very enthusiastic about the quinin-ergotin treatment which he devised several years ago. He gives quinin hydrobromate, 5 grains, and ergotin, 1 grain in gelatin coated pills four times a day. All of the foregoing clinicians insist on rest from work and mental relaxation as part of the treatment.

Plummer<sup>22</sup> has recently abstracted the histories of the unusually large number of cases treated at the Mayo Clinic, and on the basis of averages has arranged the symptoms in the order of their onset as follows: (1) cerebral stimulation, (2) vasomotor disturbances of the skin, (3) tremor, (4) mental irritability, (5) tachycardia, (6) loss of strength, (7) cardiac insufficiency, (8) exophthalmos, (9) diarrhea, (10) vomiting, (11) mental depression, (12) jaundice, (13) death. Of especial interest is the work of Rudinger<sup>23</sup> on the nitrogen minimum in hyperthyroidism. He places his patients on Landergren's low nitrogen diet, and found the nitrogen output to be so much greater than in normal persons that he considers there is a 100 per cent increase in the destruction of body nitrogen on the fourth day of the diet. In regard to the discussion as to whether we are dealing with a hypersecretion or abnormal secretion of the thyroid, it may be well to call attention to the statement of Magnus-Levy, "The quantitative relations:

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18 Rogers, John, and Beebe, S. P. The Treatment of Hyperthyroidism by a Specific Cytotoxic Serum, *THE ARCHIVES INT. MED.*, 1908, II, 297.

19 Beebe, S. P. The Serum Treatment of Hyperthyroidism, *Jour. Am. Med. Assn.*, 1915, LXIV, 413.

20 Rogers, John. The Course of Acquired Disease of the Thyroid Gland and the Principles which Seem to Control Its Progress, *Ann. Surg.*, 1914, p. 281, Exophthalmic Goiter and Its Treatment, *New York State Jour. Med.*, 1915, XVI, 4, *Am. Jour. Physiol.*, 1915, XXXVI, 113, *ibid.*, 1915, XXXVII, 121, 453, *ibid.*, 1915, XXXIX, 154, *ibid.*, 1916, XXXIX, 345.

21 Forchheimer, F. Exophthalmic Goiter in *Therapeutics of Internal Diseases*, 1913, III, 895.

22 Plummer, H. S. The Clinical and Pathologic Relationships of Hyperplastic and Nonhyperplastic Goiter, *Jour. Am. Med. Assn.*, 1913, LXI, 650.

23 Rudinger. Ueber den Eiweissumsatz bei Morbus Basedowii, *Wien. klin. Wchnschr.*, 1908, LVI, 1581.

of thyroid secretion are almost totally unknown, and are much too complicated to allow our following out a theory of hyperthyreosis in all its details, much less does it enable us to argue a theory of dysthyreosis." Falta, Newburgh and Nobel,<sup>24</sup> on the basis of experiments with various organ extracts, believe in "Ueberfunction" rather than "Dysfunction" in exophthalmic goiter, and consider that the difference in symptoms is due to differences in the constitution of the patient.

#### METHODS OF EXPERIMENT

Most of the patients studied over considerable periods of time remained in the metabolism ward described in Paper 3 of this series. They were placed in the respiration calorimeter in the morning hours, either without breakfast or after special meals, if the tests were being made to determine the specific dynamic action of food. Each patient was put in the calorimeter for half an hour or so a day or two before the first experiment, in order to let him become accustomed to the interior of the apparatus. No patient objected, since all realized that their treatment was being controlled by the results of the observations. Some of the patients had marked tremors when they moved, but inside the calorimeter they were lying quietly on a comfortable bed, and they moved but seldom. The work-adder was of great service in giving an accurate idea of the relative activity of the subject in each period. In the severe cases with moist skin, the work-adder was even more sensitive than usual, since any movement on the part of the patient liberated an abnormal amount of moisture from the bedding and clothing, expanding the air of the box to a marked degree. This accounts for some of the high readings of this instrument, but some of the patients with severe cases were distinctly restless, particularly toward the end of an observation. It was for this reason that short experiments were used by preference.

The female patients were taken directly from the general medical or surgical wards. A few of both sexes came to the calorimeter room from their homes in the neighborhood, lying down for at least two hours before the observation began. Great care was taken to avoid fatigue or excitement, since it was apparent that the metabolism of these thyroid patients showed great lability.

#### CASE HISTORIES

CASE 1—*History*—Max W. aged 40, storekeeper, born in Roumania, Hebrew, admitted Feb. 11, 1914. Had typhoid fever when 18 years old. Two years ago he was operated on for inguinal hernia. About this time he was refused life insurance because he weighed 190 pounds. He drinks little, but smokes from fifteen to twenty cigarets a day.

24 Falta, Newburgh and Nobel. *Ztschr. f. klin. Med.*, 1911, p. 72.

*Present Illness*—In January, 1913, he received news of the violent death of his brother, and was much excited for a week. The next month he suffered from a severe unproductive cough, was nervous and lost weight. He was sent to the mountains with a diagnosis of tuberculosis, but did not improve. The Wassermann reaction was found to be strongly positive, and he was treated with mercury, still without improvement. October 13, he went to Mount Sinai Hospital, where a diagnosis of exophthalmic goiter was made and medical treatment tried. Shortly afterward he went to the Presbyterian Hospital, where his protein and carbohydrate metabolism was studied by Dr. Geyelin<sup>25</sup>. It was found that the blood sugar was 109 mg per hundred c.c., the phenolsulphonephthalein output 85 per cent, the leukocytes 11,250, polymorphonuclears 68 per cent, lymphocytes 24 per cent, large mononuclears 5 per cent, and eosinophils 3 per cent. The urine showed traces of sugar, and the Wassermann test was strongly positive.

*Physical Examination*—Feb. 11, 1914, the patient is 173.7 cm tall of rather large frame with small hands and tapering fingers. The skin is dark, flushed, warm and slightly cyanotic. The beard is thick, the pubic hair normal but the hair on the chest scant and the breasts fatter than the rest of the body. The face is broad and flat, the expression angry and the eyes staring with slight protrusion. The upper lid covers about 2 mm of the cornea, but does not follow the cornea when the patient looks down. There is some weakness of convergence, he winks but seldom, and the forehead wrinkles but slightly.

There is moderate soft enlargement of the thyroid, especially the right lobe. The neck measures 37 cm in circumference. The apex of the heart is in the fifth space 11 cm to the left of the midline, and the limit of dulness 12.5 cm to the left. The action is rapid and shows a marked irregularity, apparently respiratory in type, with long pauses at the end of expiration. There is a soft systolic murmur at the apex. Carotid pulse is large, radial small. The hands show red areas on the thenar and hypothenar eminences, and there is a tremor when he is excited. There is a scar of an old left inguinal hernia operation, and the left testis is very small and soft, the right testis is large, but of normal consistency. His disposition is nervous, he is excitable, quick in thought and action, and he takes malicious pleasure in teasing his fellow patients, a cretin and a pituitary patient, both somewhat slow mentally.

*Treatment and Course*—The data concerning the food and urine are given in Table 2. In February and March the temperature was between 98.4 and 100, the pulse 110-140, the respirations from 26 to 28. March 18, the patient had an acute follicular tonsillitis with a transient rise in temperature to 103.2. Two days later it was normal. During April the temperature was below 99.6, the pulse 104-124, respirations from 20 to 22. Blood pressure, February 15, systolic, 150, diastolic, 70, March 7, 130-60, April 6, 132-82, April 23, 148-74. Beebe's serum was begun, March 5, and the doses slightly increased from time to time. The patient received twenty-three doses up to April 30, and after this the serum was given by Dr. Beebe, himself, at fairly regular intervals. With the serum he was given 1 gram of potassium iodid twice a day. The local reaction from the injection was at times quite marked but the patient felt so much better that he cheerfully submitted to the discomfort and was enthusiastic about the treatment.

During his stay in the hospital he averaged about three stools a day. He improved distinctly even before he received any treatment other than rest in bed and good food. The diarrhea stopped as did the sweating and he was not so nervous. There was slight glycosuria after 100 gm of glucose. A note April 15 says he weighed more than on admission that he was eating more and was feeling stronger each day. It was noticed that he had a polyuria.

<sup>25</sup> Geyelin H. R. The Carbohydrate Metabolism in Hyperthyroidism as Determined by Examination of Blood and Urine. *THE ARCHIVES INT MED* 1915 **LVI** 975.



TABLE 2—CLINICAL DATA IN CASE 1

Date	Temperature		Total Calories Food	Carb., Gm	Fat, Gm	Food N	Urine N	Body Weight	Urine Volume cc
	Max	Min							
2/13/14	99.6	98.6	2,971	176.0	179.0	15.7	14.88		2,775
2/14/14	99.6	98.6	3,075	220.0	231.0	21.5	15.57	62.24	2,500
2/15/14	99.6	98.6	4,091	280.0	282.0	21.5	14.88	62.00	2,450
2/16/14	99.4	98.2	3,662	280.0	288.0	19.7	12.60	61.76	2,520
2/17/14	99.0	98.6	4,321	289.0	275.0	23.5	18.15	61.89	3,150
2/18/14	100.0	98.6	3,971	313.0	228.0	18.0	15.75	62.62	3,720
2/19/14	99.6	98.6	3,970	273.0	299.0	21.5	19.25	61.81	2,720
2/20/14	99.6	98.6	3,620	299.0	201.0	20.0	17.17	61.60	3,240
2/21/14	99.0	98.6	3,801	67.0	198.0	17.6	15.58	62.26	3,015
2/22/14	99.8	98.8	3,758	289.0	216.0	21.6	18.16	62.27	3,820
2/23/14	99.6	99.0	3,574	292.0	226.0	22.6	16.19	62.28	3,240
2/24/14	99.6	99.0	3,628	274.0	212.0	21.0	17.46	61.77	3,200
2/25/14	99.8	99.2	2,411	187.0	119.0	20.9	19.91	61.17	2,890
2/26/14	99.4	98.6	4,246	310.0	222.0	22.7	17.73	61.03	2,860
2/27/14	100.0	98.6	2,533	263.0	121.0	18.0	17.86	60.90	2,990
2/28/14	99.2	98.4	3,520	271.0	205.0	19.8	14.37	60.71	2,610
3/ 1/14	99.2	98.8	3,399	284.0	181.0	20.0	15.60	60.71	3,320
3/ 2/14	99.6	98.4	2,809	199.0	157.0	20.0	18.21*	60.52	3,240
3/ 3/14	99.8	98.6	3,739	200.0	215.0	21.4	18.21*	60.29	3,150
4/ 4/14	99.8	99.0	2,842	211.0	169.0	15.7	14.59*	60.06	2,375
3/ 5/14	99.8	98.6	3,396	255.0	199.0	19.6	17.15*	60.10	2,830
3/ 6/14	99.6	99.0	3,796	273.0	207.0	20.2	12.61*	60.10	2,000
3/ 7/14	99.8	98.8						60.14	
3/22/14	99.0	98.0							
3/23/14	99.1	98.8	2,328	103.0	121.0	16.0	12.16	59.25	3,136
3/24/14	99.0	98.2	3,766	232.0	198.0	19.2	10.59		1,940
3/25/14	99.2	98.4	3,475	301.1	187.0	19.5	11.39		3,200
3/26/14	98.4	98.4	3,408	264.0	196.0	19.6	11.27	60.01	2,890
3/27/14	99.2	98.0	3,494	305.0	187.0	19.1	11.10	60.06	2,490
3/28/14	98.4	98.4	3,640	294.0	206.0	20.0	12.36	60.12	2,960
3/29/14	98.8	98.2	3,891	333.0	214.0	20.9	11.54	60.56	3,365
3/30/14	98.8	98.4	3,560	368.0	164.0	20.4	11.32	61.00	3,460
3/31/14	99.2	98.6	2,976	393.0	195.0	21.5	13.04	61.18	2,500
4/ 1/14	99.6	98.6	4,294	437.0	213.0	20.2	12.11	61.37	2,390
4/ 2/14	98.6	98.0	4,216	422.0	212.0	20.0	12.19	61.88	2,600
4/ 3/14	98.8	98.6	4,232	419.0	215.0	20.2	11.60	61.88	2,900
4/ 4/14	99.6	98.4	4,205	405.0	217.0	20.6	11.85	61.91	2,320
4/ 5/14	99.4	98.4	4,444	435.0	225.0	21.8	12.53	62.26	2,970

\* Average feces N per day March 2 to 6, 3.67 gm

TABLE 2—(Continued)

Date	Temperature		Total Calories	Carb, Gm	Fat, Gm	Food N	Urine, N	Body Weight	Urine, Volume, cc
	Max	Min							
4/ 6/14	99.2	98.4	3,316	379.0	144.0	16.3	13.10	62.26	2,790
4/ 7/14	98.4	98.4	4,529	425.0	214.0	20.3	13.09	62.26	3,060
4/ 8/14	99.0	98.4	4,506	433.0	237.0	20.0	12.62	62.62	2,660
4/ 9/14	98.8	98.4	4,345	444.0	214.0	20.7	12.17	62.90	3,190
4/10/14	98.8	98.4	4,538	424.0	242.0	20.2	13.17	63.19	3,200
4/11/14	99.6	98.2	4,062	372.0	216.0	20.0	13.28	63.32	2,500
4/12/14	99.8	98.2	4,568	401.0	253.0	21.6	11.85	63.45	2,330
4/13/14	98.8	98.6	4,801	550.0	213.0	22.0	17.54	63.01	3,770
4/14/14	98.4	98.4	4,103	408.0	213.0	20.9	12.55	62.58	1,420
4/15/14	98.4	98.4	4,232	406.0	219.0	20.6	15.58	62.92	1,390
4/16/14	99.6	98.4	4,136	388.0	217.0	20.0	15.64	63.26	1,500
4/17/14	99.6	98.8	4,164	343.0	241.0	20.1	15.02	63.58	1,330
4/18/14	99.2	98.4	4,319	355.0	249.0	21.1	15.36	63.58	1,660
4/19/14	99.4	98.8	4,108	380.0	217.0	20.8	14.85	63.58	1,580
4/20/14	99.0	98.8	3,981	350.0	217.0	20.6	15.60	63.90	1,860
4/21/14	99.2	98.4	3,817	319.0	214.0	20.2	14.18	63.81	1,600
4/22/14	99.6	98.6	4,041	369.0	214.0	20.8	17.23	63.73	1,800
4/23/14	98.8	98.4	4,353	399.0	230.0	22.6	17.85		1,980
4/24/14	98.6	98.0	2,943	280.0	151.0	15.1	14.27	63.29	1,889
4/25/14	99.0	98.6	4,064	375.0	214.0	20.7	14.40		1,620
4/26/14	99.4	98.2	4,071	369.0	217.0	20.9	15.52		1,840
4/27/14	99.2	98.2	4,107	361.0	215.0	20.9	15.19	64.56	1,850
4/28/14	98.8	98.2	3,997	360.0	214.0	20.6	14.55		2,360

and the salt in the diet was cut down to from 3 to 4 gm a day. Two days after this change the urine volume rose to 3,900 cc, with 22 gm sodium chlorid in twenty-four hours. After this the volume dropped markedly. By April 24 he was able to be up and about most of the day without fatigue. When he left the hospital the thyroid gland and the eyes were as on admission, but the heart action was regular most of the time.

A year later, April 22, 1915 he spent another day in the metabolism ward and went into the calorimeter again. He had done very well under Dr Beebe's treatment gaining 22 pounds in weight. He was able to work in his store eight or ten hours a day and a few weeks ago walked 5 miles. He seldom has palpitation but does not try to walk upstairs. He is not so excitable as a year ago. He is able to wear a collar one size smaller than last year. He looks much fatter and stronger, but the eye symptoms are unchanged and the skin is still moist and warm. The apex of the heart is maximum in the fifth space 13.3 cm to the left of the midline and the action is so markedly irregular as to suggest auricular fibrillation, a diagnosis which is confirmed by the electrocardiogram.

CASE 2—*History*.—Edwin T. aged 20 years student admitted Feb. 24 1915 discharged May 1. At the age of 10 had an attack of acute rheumatic fever and since then has had many sore throats. Three years ago he worked

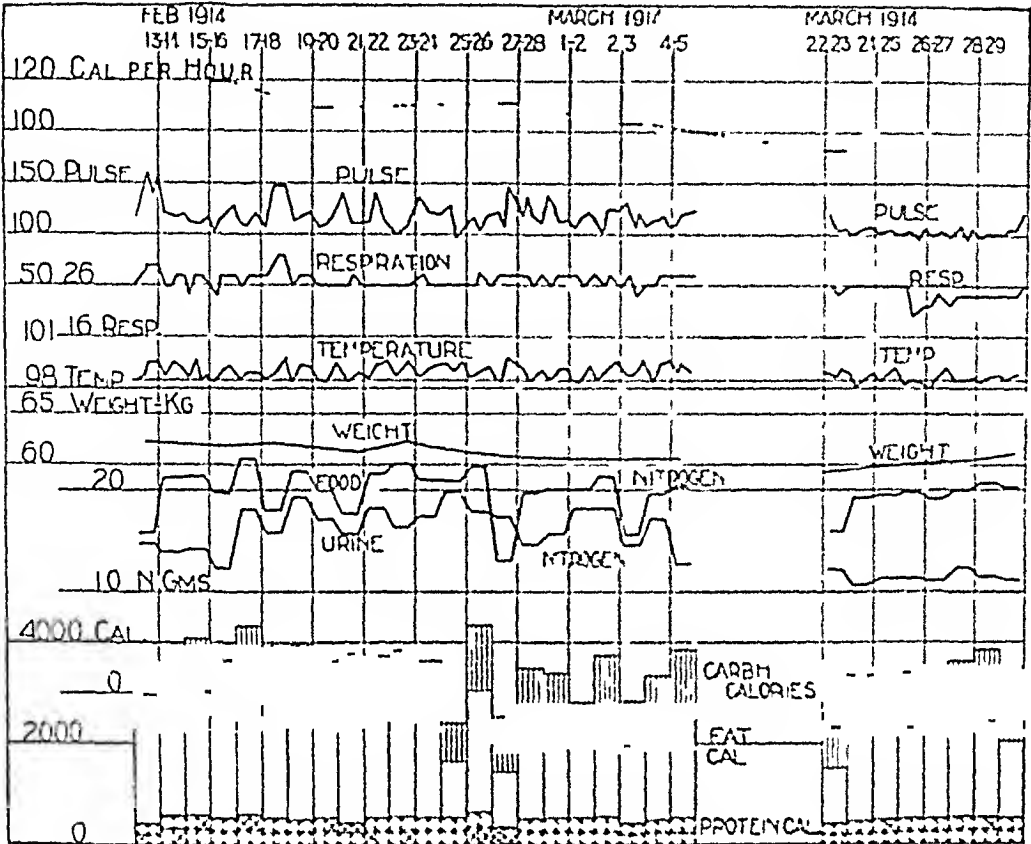


Fig 1—Chart in Case 1 Max W

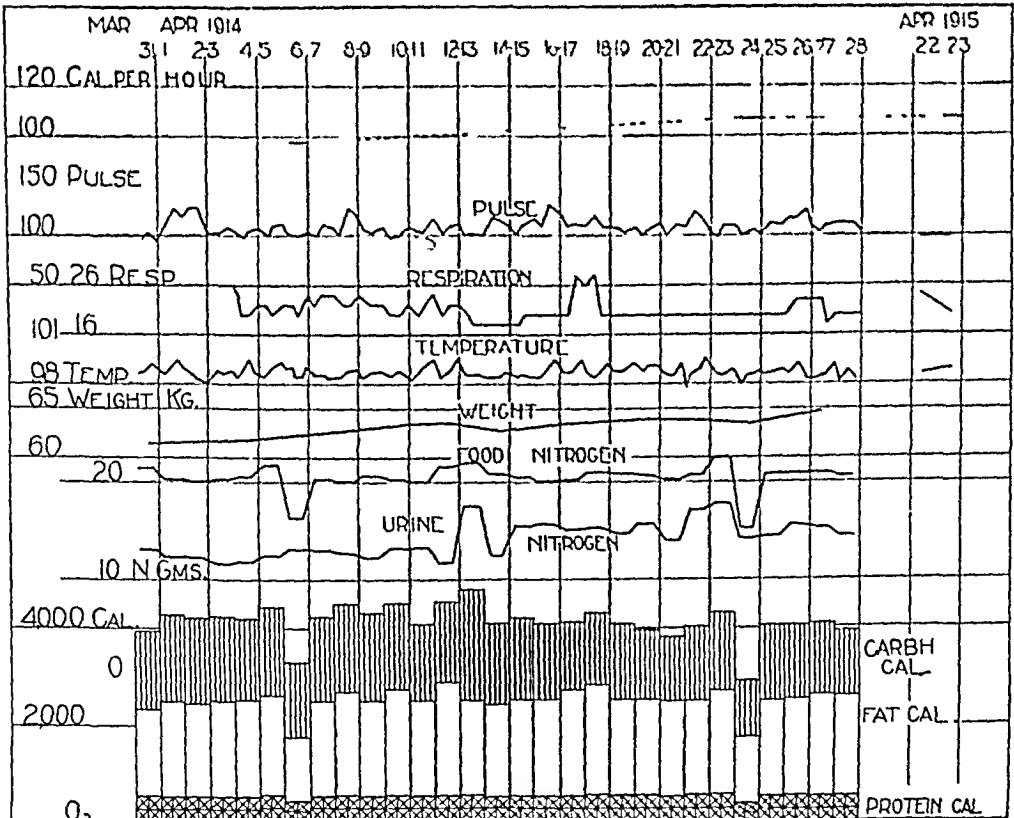


Fig 2—Chart in Case 1 Max W (continued)

very hard in school. At this time he was able to participate in track athletics. He has been accustomed to taking about six cups of strong tea every day, and has always been nervous. About six months ago he became excitable and restless and a little later was obliged to stop work. About three months ago his friends began to speak of a change in his facial expression. He grew steadily worse until three weeks ago, when a diagnosis of hyperthyroidism was made by Dr R J Shea, and proper treatment started. He lost 13 pounds in weight, but regained most of it under Dr Shea's care.

*Physical Examination*—The patient is 168 cm tall, moderately thin, the bones are slender, and the distribution of hair is normal for his age. The facies is neurotic in type and the expression angry with slight protrusio bulbi. The tonsils are large and succulent with deep crypts. The thyroid is soft and enlarged, measuring 12 cm broad, 3 cm in the vertical direction at the isthmus and 4 cm at each lobe. The heart is not enlarged, but the first sound is of poor quality, short and sharp, and there is a murmur over the pulmonic area which resembles a hemic or extracardiac murmur. The heart action is forcible, but the radial pulse small. The skin is flushed, warm and moist, often breaking out into sweat. There is a tremor when he is excited.

*Treatment and Course*—The first month in the hospital he was given no medication but kept quiet in bed. He became less and less excitable, the skin became cooler and drier and he was happy and helpful in the ward. About March 10 he began to be homesick and at times excitable. March 23, Beebe's serum was started in 5 minim doses almost every day. March 29, there was a severe local reaction accompanied by nausea. After this the serum was given in smaller doses every three days until April 14.

The patient felt a little better after the first few doses of serum, but later grew steadily worse, becoming more depressed, discouraged and at times very nervous. Between April 7 and 21 he was much excited over some personal matters, and was hard to manage. April 21, he was removed to the surgical ward, and the right inferior thyroid artery tied under novocain anesthesia by Dr Rogers. April 23 and 29, the other three arteries were tied, the patient experiencing no pain, and scarcely ever showing a pulse rate above 100. He felt better and was up and about the ward the day after each operation.

May 10 he was readmitted for a calorimeter observation after ten days in the country. He has felt better and has slept well. The wounds are healing well and his general condition seems improved, but the physical examination is much the same as when first admitted to the hospital. For clinical data see Table 3.

*CASE 3—History*—James McE., aged 29, factory worker, admitted March 1, 1915, on the service of Dr Lockwood, with the diagnosis of exophthalmic goiter and alcoholism, at the age of 22 had an attack of appendicitis. He is a heavy smoker, drinks much tea and has periodic attacks of drunkenness lasting about a week. He has been thin, nervous and in rather poor health for the last nine years, and has been very excitable for two or three years. Seven months ago he became very nervous. Five months ago he noticed swelling of the neck, palpitation and dyspnea. At this time he had severe pains in his face not relieved by the extraction of a tooth. Two weeks ago he began to have night sweats, cough, pain in the bones, hoarseness and he lost weight rapidly.

*Physical Examination*—The patient is 166 cm tall, emaciated, restless, expression staring, skin flushed, warm and sweating, pubic and axillary hair scant. Exophthalmos moderate, von Graefe's and Moebius' signs positive. The teeth show much caries and pyorrhea. There is a marked bilateral enlargement of the thyroid gland. Thorax is poorly formed, heart apex 13 cm to left of midline, regular but markedly overacting, with a rough systolic murmur, loudest to the left of the sternum. Pulse is Corrigan in type. There is a fine tremor of fingers and tongue and a distinct odor of acetone on the breath.

TABLE 3—CLINICAL DATA IN CASE 2

Date, 1915	Food					Urine					
	Total Calo- ries	Pro- tein, Gm	Fat, Gm	Carbo- hyd., Gm	Food N	Urine N	Ex- creta N Gm †	N Bal- ance Gm	Urine Glu- cose Gm	Urine Vol., cc	Body Weight, Kg
Feb 23 26	1,107	98.7	101.7	280.9	15.79						50.15
Feb 26 27	2,100	117	144.0	263.7	9.87	15.61	10.68	-1.81		870	49.78
Feb 27 28	2,882	92.9	159.9	222.6	14.86	10.70	18.18	-7.42		920	
Feb 28 1	2,751	87.0	142.7	259.7	11.92	17.71	10.16	-1.18		1,670	49.88
Mar 1 2	704*	101.0	211.6	224	16.16	18.44	26.07	-9.91		1,040	
Mar 2 3	3,462	86	184.3	279.9	15.78	16.98	18.79	-2.78		660	
Mar 3 4	3,641	104.6	188.6	255.6	16.7	17.80	19.17	-2.37		1,065	49.78
Mar 4 5	3,221	93.2	172.9	279	14.91	16.42	17.91	-2.00	10.44	1,000	49.40
Mar 5 6	2,897	132.1	125.9	288.9	22.10	19.51	21.75	-2.24	14.71	1,062	50.42
Mar 6 7	2,763	85.5	141.1	268.7	13.68	18.15	19.52	-1.37	15.15	1,755	50.04
Mar 7 8	3,760	111.0	216.2	221.6	17.70	15.55	17.25	-1.70	5.31	1,025	50.7
Mar 8 9	2,690	155.9	172.9	183.7	24.94	21.22	2.71	+1.2	7.62	1,627	50.66
Mar 9 10	3,517	105.8	194.6	211.2	16.92	6.87	8.26	-1.39	0	1,000	50.33
Mar 10 11	2,419	69.1	124.6	248.9	11.06	13.79	14.70	-1.01	18.06	1,018	49.12
Mar 11 12	3,549	160.1	204.8	302.5	16.01	15.13	16.75	-1.62	7.20	1,620	
Mar 12 13	3,725	97.1	204.1	289.8	15.53	11.35	12.90	+1.55	7.41	1,075	50.05
Mar 13 14	3,728	99.5	221.8	266.7	15.92	14.68	16.27	-1.59	9.51	1,160	50.18
Mar 14 15	3,638	97.6	199.1	288.4	15.61	15.24	16.89	-1.19	7.80	1,260	50.10
Mar 15 16	2,075	66.9	194.5	212.3	10.70	11.89	12.87	-1.17	5.57	880	50.11
Mar 16 17	3,180	66.5	205.3	213.4	10.61	13.28	14.54	-1.26	6.87	1,170	49.76
Mar 17 18	3,159	67.9	202.3	243.6	10.86	8.88	9.97	-1.10	4.62	800	50.01
Mar 18 19	3,200	70.7	203.3	248.3	11.34	12.53	13.66	-1.13	9.37	1,040	
Mar 19 20	3,550	69.8	218.0	301.8	11.16	11.49	12.60	-1.11	11.87	1,090	50.28
Mar 20 21	3,631	61.9	253.1	246.9	10.38	10.23	11.27	-1.04	8.24	980	50.28
Mar 21 22	3,467	72.9	209.3	298.7	11.66	12.61	13.78	-1.12	8.96	1,230	50.27
Mar 22 23	3,281	65.0	226.1	222.2	10.40	12.75	13.79	-1.04	14.52†	946	49.22
Mar 23 24	3,305	66.1	203.4	278.5	10.58	10.09	11.15	-1.06	8.88	815	49.98
Mar 24 25	3,466	65.8	225.0	268.9	10.52	9.47	10.52	-1.05	6.87	720	50.18
Mar 25 26	3,591	66.8	227.0	291.1	10.68	9.47	10.51	-1.04	8.00	920	50.24
Mar 26 27	3,836	66.0	256.2	288.0	10.56	10.03	11.09	-1.06	9.24	880	50.17
Mar 27 28	3,639	65.6	247.0	261.8	10.50	9.58	10.63	-1.05	3.08	710	49.94
Mar 28 29	4,194	71.3	269.2	341.0	11.40	10.65	11.79	-1.14	8.13	820	50.00
Mar 29 30	3,681	81.6	219.1	314.2	13.05	9.72	11.03	+1.31	14.50	930	50.00
Mar 30 31	3,602	70.2	118.8	302.1	11.23	10.93	12.05	-1.12	24.51	1,040	50.30
Mar 31 1	2,922	74.1	162.7	269.6	11.86	11.57	12.76	-1.19	15.90	780	50.30
Apr 1 2	3,874	96.1	214.0	363.3	15.38	13.03	14.57	+1.54	11.42	1,100	50.35
Apr 2 3	3,866	96.9	200.0	392.5	15.50	12.50	14.05	+1.55	8.20	1,250	50.63

† Urine N plus 10 per cent of food N

TABLE 3—(Continued)

Date, 1915	Food					Urine					Body Weight, kg
	Total Calo- ries	Pro- tein, Gm	Fat, Gm	Carbo- hyd., Gm	Food N	Urine N	Ex- creta N, Gm	N Bal- ance, Gm	Urine Glu- cose, Gm	Urine Vol., cc	
Apr 5 6	3,549	89.9	192.4	330.2	14.38	10.73	12.17	+2.21	11.30	970	
Apr 6 7	3,871	94.2	195.0	407.5	15.07	10.37	11.88	+3.19	8.61	800	50.90
Apr 7-8	3,758	98.9	197.5	369.9	15.82	11.71	13.29	+2.53	7.53	910	50.75
Apr 8 9	3,908	99.4	193.6	414.7	15.90	11.49	13.08	+2.82	17.22	960	51.15
Apr 9 10	3,532	99.2	211.0	283.6	15.87	12.05	13.64	+2.23	9.77	1,260	51.38
Apr 10 11	3,874	98.6	215.4	357.7	14.79	?			?	?	51.16
Apr 14 15	4,109	105.2	195.5	453.6	16.83	11.21	12.89	+3.94	15.65	1,120	51.48
Apr 15 16	3,303	83.5	195.6	278.6	13.36	11.04	12.38	+0.98	17.0	1,160	
Apr 16 17	3,803	88.4	221.4	351.7	14.14	11.66	13.07	+1.07	14.9	1,390	51.49
Apr 17 18	3,392	99.6	163.2	157.6	15.94	11.77	13.36	+2.58		1,185	
Apr 18 19	3,623	98.5	179.5	378.1	15.76	11.43	13.01	+2.75		960	51.59
Apr 19 20	3,494	88.5	166.2	386.5	14.16	12.33	13.75	+0.41	16.4	1,040	51.40
Apr 20 21	3,769	98.0	181.8	408.8	15.68	12.55	14.12	+1.56		1,050	51.38

\* Food approximate on these two days

*Treatment and Course*—For the first twelve days in the hospital he was kept in bed without medication and improved slowly. March 14, after the first observation in the calorimeter, the Forchheimer ergotin and quinin hydrobromate treatment was begun. He continued to improve slowly in general condition, and gained 6 pounds in weight. The blood pressure was 130-65 and 146-66 mm Hg. The Wassermann reaction was weakly positive, the urine contained a trace of albumin and a few casts. Temperature 99-100, pulse 108-124 up to March 15, then 82-100.

April 8, he was transferred to the surgical wards, and one superior thyroid artery was ligated under local anesthesia. May 2, one inferior thyroid artery was exposed, but the pulse became so rapid and feeble that the wound was hastily sutured without an attempt being made to ligate the vessel. The patient continued to improve slowly. May 14, the left limit of cardiac dulness was 11 cm to the left of the midline, the murmur was unchanged. The general condition was better than a month before. For clinical data see Table 4.

Notice of his death in February, 1916, has just been received.

*CASE 4—History*—Dr G S L, aged 52, physician, had typhoid fever twenty-five years ago. He smoked from six to nine cigars a day. His eyes have always been prominent. Three or four years ago when his weight was about 215 pounds he noticed a slight tremor of the hands and slight dyspnea and palpitation on exertion. About one year ago the neck increased in size. The four thyroid arteries were ligated in January, 1914 (three months ago) but he was nearly exsanguinated by a secondary hemorrhage from the superior thyroid artery. He was given quinin hydrobromate for a month but developed cinchonism. Thyroidectomy in September made him worse. For the last week he has had no treatment.

*Physical Examination*—April 9 the patient is 180 cm in height tall and large framed. The expression is staring, the skin flushed, warm, moist, smooth and slightly darkened. Dermatographia is present. There is no hair on the chest. There is moderate protrusion of the bulli, slight von Graefe's sign, convergence

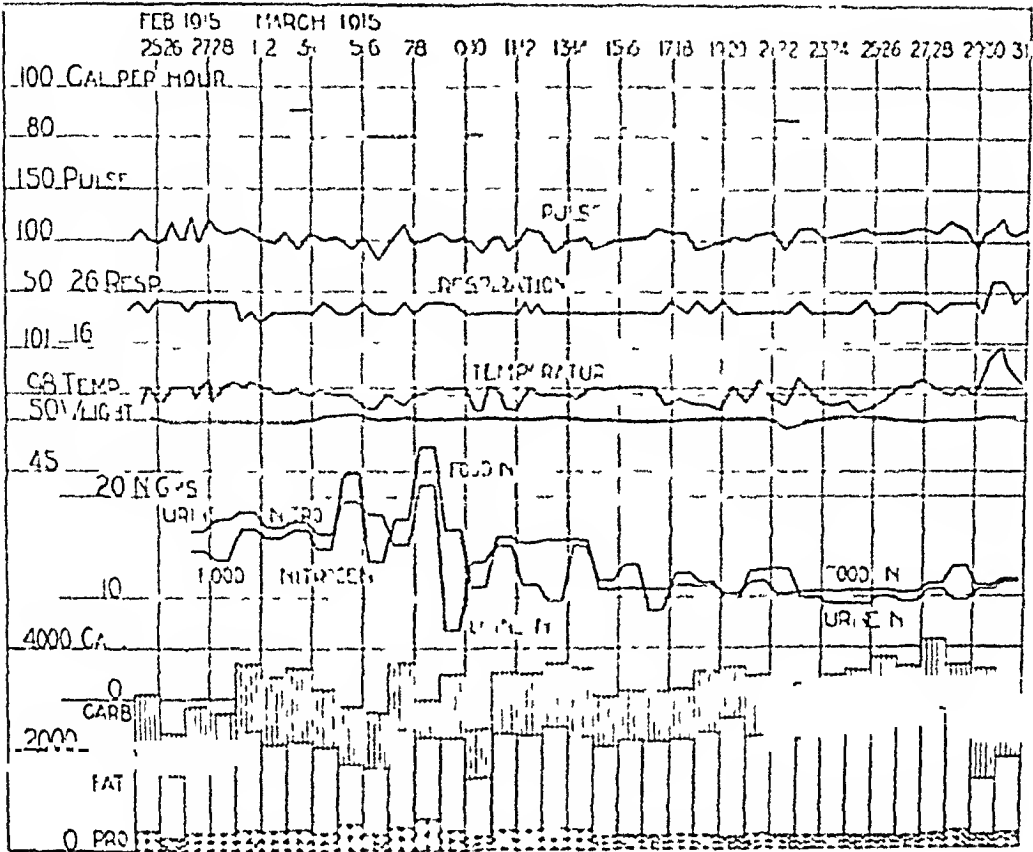


Fig 3—Chart in Case 2 Edwin T

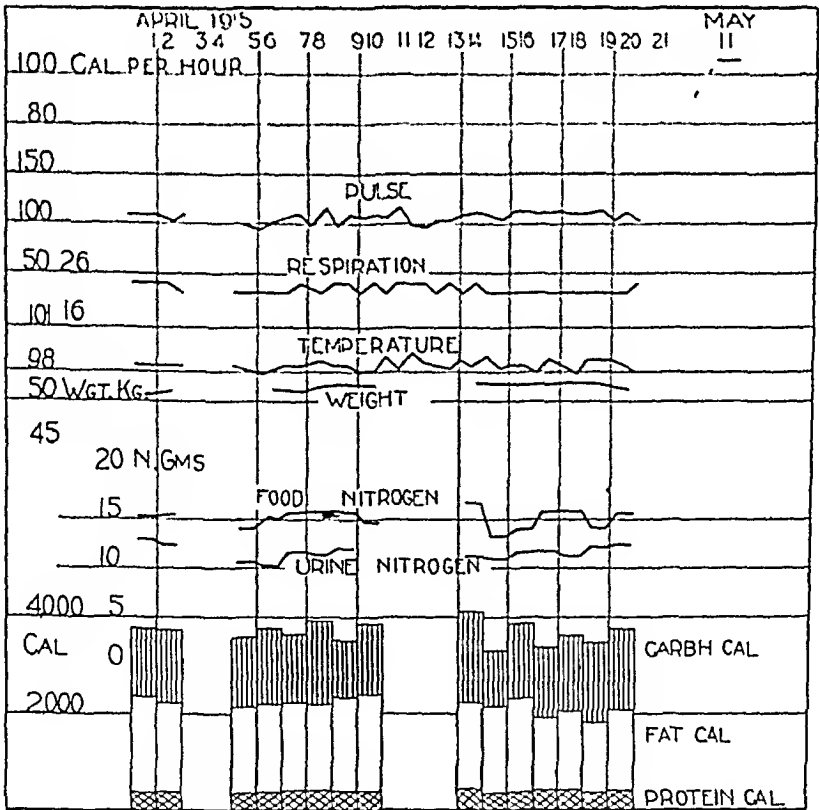


Fig 4—Chart in Case 2 Edwin T (continued)

weak thyroid lobes and isthmus enlarged Heart apex impulse is 16 cm from midline, action regular and heaving There is a soft systolic murmur maximum in the pulmonic region Pulse is 100, of large size Blood pressure is 148 mm There is a marked tremor of the hands and tongue and also of the legs when standing

*Treatment and Course*—After the calorimeter observation, April 9 the patient was given Dr Rogers' thyroid "residue," 1 c c, twice a day until April 16, when he returned for another test, his condition being unchanged except that the heart action was perhaps a little quieter

In October, 1914, a thyroidectomy was performed The day after the operation the temperature rose to 101 the pulse to 150, and the respirations to 70 per minute He died a week later

TABLE 4—CLINICAL DATA IN CASE 3

Date, 1915	Food					Urine					
	Total Calo- ries	Pro- tein, Gm	Fat, Gm	Carbo- hyd., Gm	Food N	Urine N	Ex- creta N, Gm †	N Bal- ance, Gm	Urine Glu- cose, Gm	Urine Vol., c c	Body Weight, kg
Mar 9 10	3,322	100.7	183.0	294.5	16.11	11.94	13.55	+2.56	0	1,470	41.39
Mar 10 11	3,315	94.1	178.7	309.1	15.06	13.51	15.02	+0.04	0	1,380	41.84
Mar 11 12	3,189	93.7	182.5	270.3	15.00	14.18	15.68	-0.68	0	1,695	41.26
Mar 12 13	2,558	86.2	145.9	206.9	12.79	15.09	16.47	-2.68	0	1,390	41.16

† Urine N plus 10 per cent of food N

CASE 5—*History*—Peter N. aged 23 with atypical exophthalmic goiter (?), mechanic, admitted April 9, 1915, discharged April 25 His father is 6 feet 4 inches tall (193 cm) The patient has had sore throat several times He grew very fast between the ages of 15 and 18 At the age of 18 he became weak and nervous, losing his temper easily He suffered from severe headaches two or three times a week and his hands grew so tremulous that he has been unable to work for the last year About a year ago he was in the Massachusetts General Hospital, where his respiratory metabolism was studied by Dr Means and found to be within normal limits The superior thyroid arteries were tied, and since then the headaches have been less frequent and the hands drier He is not much stronger, and he sleeps only two or three hours a night

*Physical Examination*—April 25, 1915 the patient's height is 6 feet 2 inches (187.7 cm) He is tall and thin with no suggestion of acromegaly The hands are tapering The expression is anxious, there are no eye symptoms The thyroids are soft and slightly enlarged The hands and feet are sweating, dermatographia marked Cardiac dullness extends 12 cm to the left of the midline Electrocardiograms show a slight respiratory arrhythmia There is a marked tremor of the right hand and slight tremor of the left Roentgenoscopy reveals a normal sella turcica There is a trace of glucose in the urine During his short stay in the hospital there was no change in his condition For clinical data see Table 5

CASE 6—*History*—Anna K., aged 26 single born in Ireland nurse admitted April 27 1914 whose mother, one brother and one sister are nervous had acute rheumatic fever at 16 and has had one attack of severe tonsillitis For the last ten years she has been high-strung and easily frightened For several years she has had dyspnea and palpitation on exertion About December 1913 all of these symptoms grew worse, and she began to have severe headaches scanty menses marked sweating and polyphagia and polydipsia In February 1914 she was badly frightened in a runaway and the symptoms increased in severity She has lost 15 pounds in weight



For the last two months she has been given thyroid "residue" by Dr Rogers April 4 both superior arteries were ligated by Dr Rogers in Bellevue Hospital

*Physical Examination*—The patient is very thin, frame small expression tired and neurotic, speech jerky and ignited voice weak. Skin moist. Exophthalmos slight eyelids puffy, no von Graefe's sign tongue and hands tremulous. Thyroid moderately enlarged especially on the right. Cardiac impulse diffuse maximum in the fifth space 8.5 cm to the left of the midline. Action rapid and regular.

*Treatment and Course*—After the first calorimeter observation the two inferior thyroid arteries were ligated April 29. May 13 the patient returned to the calorimeter room for the day feeling less nervous and more ambitious than before. June 22 she reported to Dr Rogers weighing 112 pounds pulse 90 general condition much improved.

TABLE 5—CLINICAL DATA IN CASE 5

Date 1915	Food					Urine					
	Total Calo-ries	Pro-tein, Gm	Fat Gm	Carbo-hydr Gm	Food N	Urine N	Ex-creted N Gm †	N Bal-ance Gm	Urine Glu-cose Gm	Urine Vol, cc	Body Weight kg
Apr 10 11	2,012	85.0	103.4	238.5	17.44						63.95
Apr 14 15	2,500	66.2	137.1	190.5	10.00	12.17	13.2	-2.04	Slight trace	747	63.14
Apr 15 16	2,803	105	170.2	230.1	11.12	12.16	11.27	-2.15	Trace	840	61.09
Apr 17 18	2,912	87.3	160.6	215.8	13.97	12.71	14.74	-0.87		1,100	
Apr 18 19	2,757	79.2	115.1	274.6	11.71	11.91	13.11	-1.40		1,240	65.18
Apr 19 20	2,808	72.7	100.5	161	11.6	11.91	12.65	-1.02	Trace	1,080	64.61
Apr 20 21	3,023	74.7	171.6	271.4	11.94	11.10	12.60	-0.71		1,160	65.28
Apr 21 22	2,711	83.3	149.5	229.6	11.22	11.82	12.13	-0.19	Trace	1,420	64.65
Apr 22 23	2,165	81.9	177.8	203.7	13.78	12.95	14.51	-0.73	Trace	1,300	61.52
Apr 23 24	3,006	85.6	189.3	218.1	13.70	12.81	11.18	-1.57	Heavy trace	1,000	64.20
Apr 24 25	2,817	87.3	171.6	210.9	13.97	12.61	11.01	-0.01	7.21	1,300	64.45

† Urine N plus 10 per cent of food N

*CASE 7—History*—Anna R. aged 29, unmarried cook and saleswoman, born in Ireland, admitted May 8, 1913, discharged June 5 five years ago had typhoid fever and shortly afterward noticed swelling of her throat. A year or so later her tonsils were removed by a doctor who told her she had a goiter. Since the attack of typhoid she has had at times tremor, palpitation, restlessness and loss of weight. She thinks she has improved during the last two years. A year or so ago her friends noticed that her eyes were staring. She has been able to work up to the time of admission.

*Physical Examination*—The patient is tall and thin, exophthalmos present, von Graefe's and Stellwag's signs present. There is slight tremor of hands and tongue. The heart is slightly enlarged, first sound of poor quality. The thyroid is moderately enlarged.

*Treatment and Course*—May 8 to 11 temperature is normal, pulse from 84 to 88 respiration from 20 to 22. The first calorimeter observation was on May 10. On the 12th under local anesthesia Dr Rogers ligated the left superior and right inferior thyroid arteries and removed the tip of the left upper pole. May 16, the two other vessels were ligated and the tip of the right pole removed. After the first operation the temperature was 99 to 100, pulse 100-112 respiration 24 to 26. After the second operation she was given half a grain of the

Loomis Laboratory special thyroid extract every four hours until May 18. She menstruated from May 16 to May 19. For three days after the operation the temperature was 99 to 102, pulse 96-130, respiration 24 to 32. By May 20, at the time of the second calorimeter observation, the temperature was almost normal. By May 25 she was up and about the ward.

After leaving the hospital she spent two months in the country and gained weight up to 117 pounds. Since then she has been at work and has lost 2 pounds, but has not felt nervous except when she works hard. May 14, 1914, she returned for a calorimeter observation. The scars of the operation were well healed, the left lobe and isthmus of the gland were moderately enlarged and the right lobe considerably enlarged. She was still thin and nervous, and the voice weak and husky, but she looked a little better than a year ago.

A week or so after the last calorimeter observation she was married, and did well until her husband lost his job on account of the war. She started work in the store again, and her weight dropped to 104 pounds and all the symptoms returned. In March, 1915, she reported at the ward very thin, very nervous, hands very tremulous, skin moist, pulse very rapid and small.

*CASE 8—History*—Sarah M., aged 29, chambermaid, unmarried, born in Ireland, admitted April 29, 1914, discharged May 4, nine years ago came to America, and eight years ago began to suffer from loss of weight, nervousness, weakness, tremor and enlargement of the neck. Three months later she was operated on, and apparently part of the thyroid gland removed. She recovered quickly, and for the next six years enjoyed good health. One year ago she began to have a return of the weakness, nervousness and loss of weight. She became excitable, sweated easily, and slept poorly. At times she had palpitation. She thinks the neck has swollen again.

*Physical Examination*—April 29, the patient is tall, fairly well nourished, and does not look sick. The eyes are a little brighter than normal, but there is no exophthalmos, no von Graefe's sign and only slight weakness of convergence. The left lobe of the thymus is absent, the right lobe moderately enlarged. There is slight tremor of the tongue and hands on excitement. The heart is not enlarged and is not overacting, pulse from 86 to 97. The skin is a little moist and not flushed.

*Treatment and Course*—The afternoon of the calorimeter observation a partial thyroidectomy was performed by Dr. Rogers. She made a rapid recovery, and when she reported in February, 1915, she had no subjective or objective symptoms.

*CASE 9—History*—Marion B., aged 22, unmarried, admitted Feb. 4, 1915, discharged February 5, was sent down from the Presbyterian Hospital, where her case was studied in detail by Dr. Gevelin. In 1912 the heart began to beat fast, she sweated easily and began to notice swelling of the neck. Four operations were performed at the Presbyterian Hospital. In July, 1913, two arteries were ligated. Two months later the right lobe of the gland was removed. In February, 1914, an appendectomy was necessary. In July, 1914, part of the left lobe of the thyroid was removed and she felt better until September, 1914, when her nervousness returned. At the time of her admission she had been menstruating four days.

*Physical Examination*—The patient is short and rather stout, excitable. She has a nervous, staring, angry expression. The exophthalmos is marked, the pupils are dilated, the skin moist, the pulse small and soft.

*CASE 10—History*—Margaret L., aged 51, married, with atypical exophthalmic goiter, auricular fibrillation and mitral insufficiency, admitted March 25, 1914, died May 19, 1914. She had three children in good health. A year ago she began to feel nervous and lost appetite and weight. She noticed a rapidly growing swelling on the right side of the neck. This was removed by operation in July, 1913. Since then she has been worse and has violent palpitation of the

heart all the time. A month ago she began to have huskiness of the voice, swollen arms and legs and much dyspnea.

*Physical Examination*—The patient is well developed and well nourished, dull mentally, slow of speech the voice husky but not brassy. Skin thick, hard dry, feels myxedematous. Slight exophthalmos, no von Graefe or Stellwag sign.

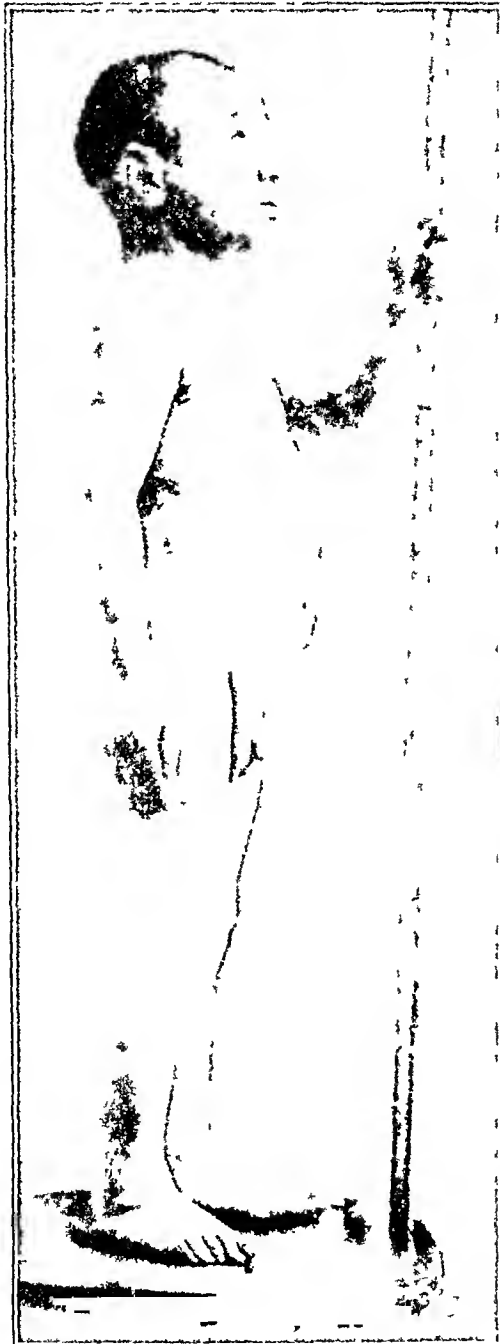


Fig. 5 (Case 12)—Benny L. Cretin holding ruler marked in inches

Right lobe of thyroid absent, left lobe slightly enlarged. Heart much enlarged with an irregularity shown by tracings to be due to fibrillation. There is a systolic murmur at the apex. There is some fluid in the right pleural cavity. She is dyspneic and looks seriously ill.

*Treatment and Course*—At first she was given thyroid 'residue,' but for three weeks before the calorimeter observation received no medication except codein and ammonium carbonate to control the cough. May 5 a small thymus gland was removed. Histologic examination showed "fatty infiltration of the thymus, thymic tissue appears normal." After the operation she developed fever, rapid pulse, grew weaker and died. There was no necropsy.

**CASE 11—History**—Miss B. H., aged 31, trained nurse, admitted April 4, discharged April 20, 1914. In childhood had pertussis, scarlet fever, measles, varioloid, mumps, bronchitis, typhoid fever at 15 years, appendicitis and peritonitis at 20, many attacks of tonsillitis and finally tonsillectomy at 22, and diphtheria at 29. For the last two or three years she has worked very hard as a nurse on difficult cases.

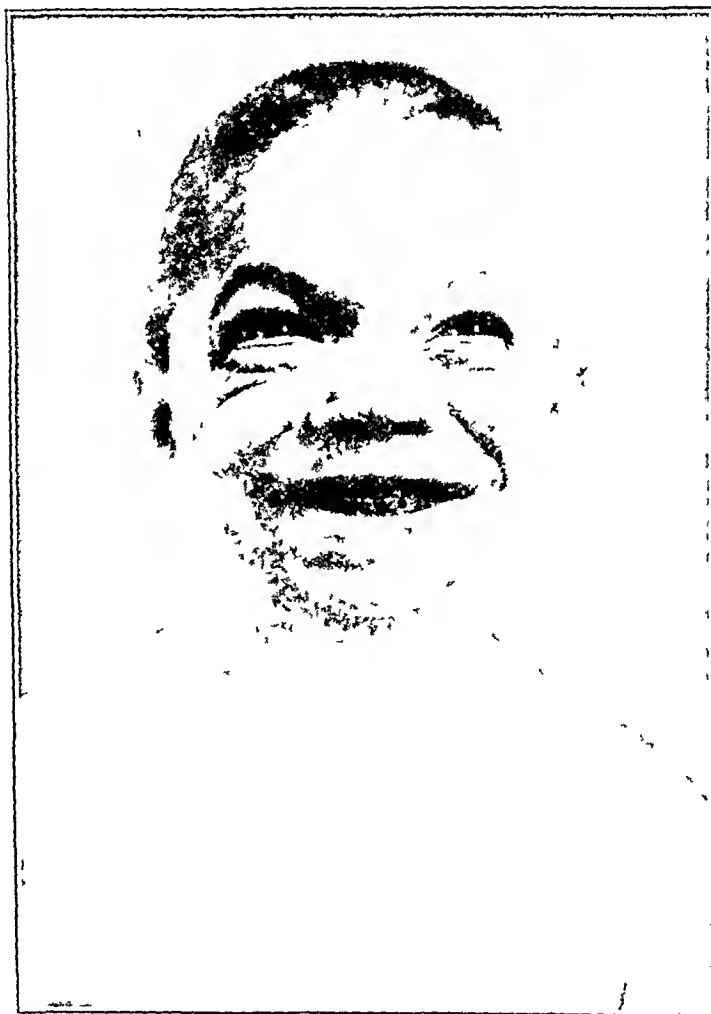


Fig. 6 (Case 12)—Benny L. Cretin 36 years old (continued)

In 1910 she noticed that the thyroid was enlarged. In August 1913, while nursing a typhoid patient she began to have severe diarrhea with eighteen movements a day. She vomited continually, the pulse was very rapid and she was excitable and weak. After prolonged rest these symptoms would clear up enough to allow her to work once more. In January 1914 the right side of the thyroid became enlarged and painful, nervousness increased and she lost 20 pounds. In February 1914 the right lobe of the gland was removed. Two days later the voice, which had been clear, dropped to a whisper and did not return to normal for a year or so. After the thyroidectomy the pulse rate dropped from an average of 140 to 72 and she has had but little palpitation and no sensation of undue

warmth. The nervousness has begun just as bad, and she has diarrhea whenever she takes rats. At the time of admission to Bellevue she was much depressed over the loss of her voice, which she feared was to be permanent.

*Physical Examination*—April 4, 1914, the patient is of moderate height (159.2 cm.) thin, looks tired and nervous, at times excitable but always anxious to cooperate in treatment or observations. There is a very slight exophthalmos, slight widening of the palpebral fissure, eyes bright, no von Graefe's sign. There is no enlargement of the isthmus or remaining lobe. The heart is normal and not rapid. There is no dermatographia but at times there is tremor.



Fig. 7 (Case 12)—Benny L. Roentgenogram of hand.

*Treatment and Course*—While in the hospital she was very nervous, slept poorly, and at times vomited. The temperature was normal, pulse 72 to 92, respiration 22 to 26. Until the completion of the second calorimeter observation April 13, she received no medicine, then thyroid "residue" 1 c.c. hypodermically twice a day until the third test. While in the hospital on a low diet containing about 4 gm. of nitrogen the urinary nitrogen was from 3 to 4 gm. a day.

After leaving the hospital she went to the country, and her appetite improved and she gained strength and did well except for a sudden severe stomatitis which loosened her teeth. In March, 1915, she reported looking thin but almost well. She is able to do light work nursing if she rests between cases. Her physician now attributes many of her symptoms during the past year to hysteria.

**CASE 12—History**—Benny L., aged 36 (?), with cretinism, Hebrew, admitted April 8, 1914, discharged May 2, was taken to the Children's Hospital on Ran-

dall's Island sixteen years ago, and during that time has had no visitors, so that his previous history is unknown. He has not changed since his admission, and he is very happy playing with the boys and going to school, where he learns practically nothing. He can write his name, dress and feed himself and he corresponds to a child of about 7 years in the Binet test. In 1906 an attempt was made to transplant sheep's thyroid into the pelvis of the left kidney and later into the abdomen. There were no favorable results. He has had numerous courses of treatment with Parke, Davis & Co thyroid extract, but on doses as small as from one-half to 1 gram three times a day develops tachycardia, weakness and often faints.

TABLE 6—CLINICAL DATA IN CASE 12 (BINNY L.)

Date	Temperature		Total Calories	Carb., Gm	Fat, Gm	Food N	Urine, N	Body Weight	Urine, Volume cc
	Min	Max							
4/ 8/14		99.2							
9/ 9/14	98.1	98.6	2,381	229.0	120.0	12.5	7.90		1,200
4/10/14	98.4	98.4	1,118	112.0	53.0	6.6	5.95	23.19	965
4/11/14	98.2	98.2	1,227	125.0	56.0	7.7	6.19		920
4/12/14	98.2	98.2	1,396	110.0	65.0	8.1	6.66		1,000
1/13/14	98.2	98.2	1,496	152.0	70.0	8.7	6.89		1,076
4/14/14	98.6	99.1	1,129	102.0	37.0	1.8	1.67	23.34	795
1/15/14	98.2	98.4	1,560	137.0	63.0	8.2	3.53		710
4/16/14	98.4	99.0	1,229	130.0	55.0	7.3	6.36		950
4/17/14	97.6	98.2	1,031	100.0	51.0	5.9	5.83	24.21	935
4/18/14	97.8	98.0	1,128	109.0	55.0	6.8	5.16		860
4/19/14	98.0	98.6	974	91.0	47.0	5.8	7.01		1,145
4/20/14	98.0	98.2	1,196	117.0	57.0	6.9	6.11		1,195
4/21/14	98.0	98.8	643	66.0	23.0	6.1	5.39	21.06	970
4/22/14	98.0	98.6	1,187	119.0	54.0	7.8	6.19		960
4/23/14	98.0	98.2	704	57.0	38.0	4.4	4.82	24.30	776
4/24/14	97.6	98.0	1,070	103.0	50.0	6.5	5.05		815
4/25/14	97.8	98.6	1,187	135.0	50.0	6.4	5.60		1,040
4/26/14	98.6	98.6	963	103.0	44.0	5.0	4.61		820
4/27/14	98.0	98.6	839	128.0	25.0	3.2	4.13	23.61	672
4/28/14	98.0	98.6	728	68.0	36.0	1.5	4.04		700
4/29/14	98.6	100.0	618	59.0	31.0	3.5	5.32		1,350
4/30/14	99.6	100.2	1,061	99.0	53.0	6.3	6.11		1,400
5/ 1/14	100.2	101.0	356	37.0	17.0			23.06	

*Physical Examination*—The patient (Figs 5-7) is short, 110.3 cm tall (3 feet 7½ inches), stout, with prominent abdomen, short, thick extremities and short pudgy hands, the face is broad, wrinkled, with thick lips, broad nose, baggy eyelids, teeth widely spaced, in poor condition with much gingivitis and pyorrhea. The thyroid is not palpable, heart normal, abdomen shows slight umbilical hernia. Scars over right kidney, skin very dry, harsh, inelastic with fine branny desquamation. There are pads of fat on each side of the neck, and others just anterior to axillae. External genitals resemble those of a boy of 7, there are no male secondary sexual characteristics. Blood pressure is 125 mm, Wasser-

mann test strongly positive, the urine contains much sterile pus, evidently due to large calculi shown by roentgen copy to be in the pelvis of the kidneys. The temperature was slightly subnormal most of the time; pulse 64-80, respiration 18.

The patient was always in good humor. He had a good sense of fun and was amused down his nose; his voice was hoarse and childish but he differed from the normal child in being able to sit quiet for hours at a time. He grew tired rather easily, his appetite was very small, his bowels constipated. April 27 in the afternoon the administration of thyroid extract was begun, 1 grain three times a day; the temperature rose to the level of 100 F., pulse 100, respiration 18, blood pressure 115. He felt limp and looked sick so that the drug had to be discontinued. For clinical data see Table 6.

## DISCUSSION OF RESULTS

### THE BASAL METABOLISM IN EXOPHTHALMIC GOITER

The determination of the basal metabolism in exophthalmic goiter is a matter of technical difficulty. The patients are excitable, restless and easily tired. For this reason great care must be used when nose or mouthpieces or face masks are employed since these may prove uncomfortable toward the end of an experiment or series of experiments. The respiration calorimeter, although perfectly comfortable for a normal person for five hours, often tires a goiter patient after three hours. Fortunately the apparatus is so delicate and accurate that the measurement of the heat production by the method of indirect calorimetry is satisfactory after a preliminary period of three-fourths hour. Experiments one hour long could be employed, but two hour observations are more satisfactory since the method of direct calorimetry is not as accurate as could be wished in the first experimental hour. This will be discussed later.

There is a distinct tendency for the patients to become more restless as the observation progresses, and it will be noted that the metabolism in the fasting experiments is usually higher in the second hour than in the first. There is also a tendency on the part of patients as well as normal controls to show a slightly higher metabolism the first time they are the subject of a real experiment, although they are all trained by a short "dummy experiment" a day or so previously. Goiter patients on some days are distinctly more disquieted than usual, and one gets the impression that on such days the increase in metabolism is due partly to the restlessness and partly to an exacerbation of the disease which causes both restlessness and increased heat production.

It has long been realized that tremor and involuntary activity on the part of goiter patients might be responsible for a considerable portion of the increase in metabolism. Magnus-Levy discussed these factors, and found that the increase in metabolism is almost as marked when the patient is sleeping or under the effect of opium. He found also that the tremor of paralysis agitans increased the oxygen consumption only from 20 to 30 per cent. A careful scrutiny of the

results reported in the present work shows that restlessness, tremor and mental irritability contribute only a small percentage of the increase in most of the cases. The activity of the patients was checked by the delicate work-adder and by careful observation. All of the patients

TABLE 7—THE INFLUENCE OF SLEEP, RESTLESSNESS, ETC., ON METABOLISM IN HOURLY PERIODS

Subject and Date	Calories per Hour Ind	Per Cent above Lowest Figure	Work Adder Cm	Behavior of Patient
Case 1 (Max W) Feb 16	114.6 124.1		31 14	A little restless. Involuntary tremor at end of period. A little restless.
Feb 20	104.9 111.2	9	16 22	Calm and quiet. Calm, slightly excited by visitor for ten minutes.
Feb 21	120.8 117.2	3	26 75	After dextrose, quiet. After dextrose, very restless.
Mar 4	101.1 106.2	5	15 78	Asleep the whole hour. Awake, pulse rapid last half hour.
April 6	92.2 99.4 101.4	8 10	25 75 51+	Quiet, asleep 50 minutes. Very restless. Very restless, uncomfortable.
April 23, 1915	102.8 111.0	8	21 33	Fairly quiet, asleep 20 minutes. Fairly quiet, asleep 5 minutes.
Case 2 (Edwin T) Mar 3	93.6 89.2	5	23 30	Quiet, reading 45 minutes. Asleep 30 minutes in 90 minute period.
Mar 6	80.2 80.2	0	6 19	Reading whole hour, very quiet. Asleep 55 minutes, fairly quiet.
Mar 10	77.4 87.3	16	16 18	Sleeping, slightly restless. Reading 55 minutes.
Mar 22	79.8 88.0 94.8	11 20	2 10 30	Sleeping, very quiet. Reading 55 minutes, quiet. Asleep.
May 11	96.2 115.1	20	15 34	Restless, stretched arms. Restless, vomited shortly after exp.
Case 3 (James McE) Mar 12	95.8 98.6 101.7	3 6	14 23 80	Reading quietly 50 minutes. Reading quietly 36 minutes. Not reading, fairly quiet.
Mar 31	88.6 95.6	8	10 26	Reading 60 minutes, quiet. Reading 32 minutes, restless.
Case 4 (Dr G S L) April 16	104.8 109.3	4	29 58	Fairly quiet. Slightly restless.
Case 6 (Anna K) April 28	102.6 101.5	1	36 38	Restless. Quieter.

were as quiet as the normal controls for at least some of the periods of observation. Most of them slept quietly during a considerable portion of some periods. When we compare the sleeping and quiet periods with those in which the patient was awake or excited or restless, we find no constant and striking increase large enough to change our inter-



TABLE 8.—SUMMARY OF RESULTS OF RESPIRATION EXPERIMENTS.

[illegible]

Case 3 (James McE ) 3/12/15	Basal	109	0.78	- 6	2.10	67.2	+91	71.1	+87	Quiet
3/31/15	Basal after quinin and ergotin	97	0.82	- 1	2.30	61.0	+81	70.7	+78	Fairly quiet
5/11/15	Basal after ligition	115	0.75	- 8	2.30	68.1	+97	76.1	+92	Fairly quiet
Case 4 (Dr G S L ) 1/ 3/14	Basal	100	0.77	- 0	1.15	16.9	+12	55.0	+38	Quiet
4/16/14	Basal after thyroid "residue"	99	0.76	- 1	1.51	51.5	+50	57.6	+15	Slightly restless
Case 5 (Peter N ) 4/14/15	Basal	71	0.83	+ 8	1.10	35.5	+ 2	38.8	- 2	Very quiet
Case 6 (Anna K ) 4/28/14	Basal after ligation of 2 arteries	121	0.75	- 5	2.30	66.1	+101			Fairly quiet
5/13/14	Basal after ligation of 2 more arteries	100	0.81	- 8	1.90	55.1	+71			Very quiet
Case 7 (Anna R ) 5/10/13	Basal	119	0.79	- 8	1.15	13.1	-131			Quiet
5/20/13	Basal after ligation		0.76	- 7	1.70	19.9	+55			
5/28/13	Basal		0.77	- 5	1.61	19.2	+52			
5/14/14	Basal 1 yr later	97	0.80	- 1	1.18	13.6	+35			Very quiet
Case 8 (Sarah M ) 4/20/14	Basal*	92	0.78	- 1	1.11	13.8	+36			Fairly quiet
Case 9 (Marion B ) 2/5/15	Basal	127	0.77	- 1	1.10	41.1	36			Restless
Case 10 (Mrs L ) 4/20/14	Basal	85	0.76	- 1	1.30	42.0	30			
Case 11 (Miss B H ) 4/ 8/14	Basal	60	0.83	+ 1	1.21	35.1	+10	10.0	+ 5	Quiet
4/13/14	Basal	74	0.81	- 1	1.19	35.1	+ 9	39.9	+ 8	Very quiet
4/18/14	Basal after thyroid "residue"	94	0.84	- 2	1.15	33.1	+ 3	37.8	+ 2	Very quiet
Case 12 (Benny L ) 4/10/14	Basal	84	0.92	+ 8	1.21	27.6	-20	33.0	-17	Very quiet
4/14/14	1 to 4 hrs after 100 dextrose	88	1.00	- 1	1.34	31.1		37.9	+15	Very quiet
4/21/14	1½ to 5½ hrs after 3.6 N e iscin	82	0.93	+ 6	1.23	28.9		31.9	+ 13	Quiet
4/23/14	Basal	78	0.87	- 0	1.09	25.6	-26	31.0	-22	Quiet
4/27/14	1 to 4 hrs after 70 dextrose	79	0.95	+ 0	1.19	27.7		33.3	+ 7	Very quiet
5/ 1/14	After thyroid extract	95	0.79	- 6	1.11	33.2	- 1	39.8	+ 0	Very quiet

\* After very small breakfast

pretation of the results. All of the experiments which show significant differences between the various periods either in the heat-production, work-adder reading or activity of the patient as noted in the protocol have been grouped in Table 7. Some of the patients were allowed to read while in the calorimeter, since it was found that they were quieter if their minds were pleasantly occupied. It will be seen that the metabolism was about the same during the reading periods as during the periods of slightly restless slumber characteristic of this disease. Edwin T. (Case 2) was the only subject who showed an increase of more than 10 per cent on account of movement. On March 10, reading seemed to increase the calories 16 per cent. March 22, the reading metabolism is about half way between that of two widely varying sleeping periods, and May 11 it rose on account of nausea in the last period.

The results of all the respiration experiments are summarized in Table 8, and the average metabolism on the days of the basal determinations compared to the normal averages discussed in the thirteenth paper of this series. It will be noted that in all the thin patients the rise above the normal is less marked when the measurements are made according to the linear formula than if Meeh's formula for the determination of the surface area be employed. If we confine our attention for the time being to the basal metabolism during the first week that the patients were in the hospital, we can compare the cases here reported with those already described in the literature. In all there is a total of forty-five patients whose respiratory metabolism has been studied, fasting and as quiet as the circumstances would permit. It has seemed best to group these in Table 1 arranging them according to the calories per square meters of surface area as calculated from Meeh's formula. The calculation of the calories has been made from the tables of Magnus-Levy,<sup>26</sup> using the oxygen consumption and respiratory quotient, assuming that protein furnished about 15 per cent of the calories. This gives a more accurate basis of comparison than the mere statement of cubic centimeters of oxygen or carbon dioxide per kilogram and minute. Still better comparisons might be made if we could use the linear formula or its modification, but this is impossible because many of the authors do not give the heights of the patients. We are similarly handicapped in the tabulation of other symptoms, since many of the clinical reports are very brief. Still it is possible to make a fairly complete chart which allows us to see which symptoms accompany the cases with high metabolism. The plus marks are necessarily my own interpretation of the author's statements.

<sup>26</sup> Magnus-Levy. Von Noorden's Handbuch der Pathologie des Stoffwechsels, Ed 2, 1906, 1, 207.

At the head of the list comes Hirschloft's patient Louise B. shortly before her death with the most extreme symptoms of hyperthyroidism. There are eight other subjects whose metabolism is greater than 50.5 calories per square meter per hour, a figure 75 per cent. above the average for women. Of these all are classified as severe or very severe, except one designated "ischlich schwer." All show a very rapid pulse, thyroid enlargement, exophthalmos, mental irritability, warmth of skin, tremor and emaciation. Eleven more patients are above the figure which represents a 50 per cent. increase in metabolism. Of these, one is classified as very severe, five are classified as severe, and five as moderately severe. With most of these the pulse rate averages over 100 and there are signs of cardiac enlargement. Gouter, mental irritability, tremor and warmth of skin are present in all. Exophthalmos is absent in one, and the emaciation is slight as a rule.

The figure 38.2 represents the upper normal limit for men, and 35.5 that for women. Between the e marks and that indicating a 50 per cent. increase there are sixteen patients, six severe, one moderately severe, four mild and the others atypical, "forme fruste" or simple gouter. In them the tachycardia is not so marked, and exophthalmos and emaciation are inconsistent. Gouter, mental irritability, tremor and warmth of skin are present. There are eight subjects within normal limits. Among these are four mild cases of exophthalmic gouter, two of simple gouter, and two cases in which operation had been performed, one of these being atypical from the start. One patient is below the normal limit. Magnus-Levy in one article classifies her case as half way between Kropf and "forme fruste," and in another article as simple gouter and refers to her as hysterical.

Age is a factor which changes our interpretation of some of the results. The boy M. P., aged 11½ years, with a small struma, is really a little below the average level for his age. Frau B. and Frl. U., aged 52 and 55, respectively, are at an age when the normal metabolism is from 5 to 10 per cent. lower than the average figure for younger women.

The patients whose metabolism is within or below the normal limits show but slight tachycardia, slight if any gouter or exophthalmos and no unusual warmth of skin. Two show mental irritability and tremor.

We must not forget that some of the symptoms of hyperthyroidism are due either wholly or in part to the increased metabolism. The sensation of unusual warmth, the hot, flushed skin and the sweating are caused by the fact that each square centimeter of skin must radiate more heat than in a normal person. These phenomena are found with an increased metabolism from almost any cause, although it is quite possible that in exophthalmic gouter they may be more marked for the same degree of increase. In like manner the loss of

weight is due to the fact that the increased heat production is not balanced by an increased caloric intake and absorption. The appetite of the goiter patient would keep the weight stationary or even cause an increase were the metabolism normal. For some reason the appetite and absorptive powers in hyperthyroidism are not quite sufficient to maintain weight, although laboring men with a much higher caloric requirement per day remain in nutritive equilibrium. This may be accounted for in part by the increased nitrogen metabolism, which is usually ascribed to a toxic destruction of protein. Part of the increase in pulse rate is also due directly to the increased metabolism which necessitates a greater blood flow. This, however, would not account for all of the increase, since muscular work, raising the metabolism from 50 to 100 per cent, seems to increase the pulse rate by only 10 to 30 beats per minute. Still we must remember in discussing the tachycardia and cardiac enlargement that the continued stimulation of metabolism in hyperthyroidism is very different from the stimulation due to muscular exercise which lasts for only a fraction of a day. If it were possible to stimulate the metabolism of a normal man twenty-four hours a day over the period of a year or more, we might perhaps reproduce the cardiac symptoms of hyperthyroidism as well as the warmth of skin and loss of weight.

The more we study the table, the more apparent it becomes that the increase in metabolism is proportional to the severity of the disease. The only exceptions in the group are found in doubtful or atypical cases, or those that have undergone operative treatment. Very severe cases show a metabolism 75 per cent or more above the average, severe cases 50 per cent or more, moderately severe and mild cases show an increase of less than 50 per cent, while a few mild and several atypical or cases in which operation has been performed are within normal limits. The degree of tachycardia, goiter, exophthalmos and mental irritability are roughly proportional to the increased heat production. Unfortunately we have not enough data to compare the level of metabolism with the degree of mononucleosis, the sugar tolerance, the drop in blood pressure from large vessels to the periphery, the eye symptoms and many others that are considered of prime importance by various authors.

#### THE RESPIRATORY QUOTIENTS

In the patients with high basal metabolism, the respiratory quotients are necessarily low after a fast of seventeen hours or more. Most of them are close to the figure of 0.77, which indicates that about 17 per cent of the calories are derived from the combustion of carbohydrates. With normal men the quotient under similar conditions varies rather widely, but averages 0.82, showing that about 32 per

cent of the calories are derived from carbohydrates. Therefore gutter patients who are kept in bed in the hospital evidently have less available glycogen after a fast of seventeen hours than normal men who have been up and about during the evening and morning before the experiment. This may be due either to the fact that the thyroid patients have insufficient appetites and store the evening with a smaller store of glycogen or else that they use up the starch of the food and the stored glycogen more rapidly than the controls. The respiratory quotients here reported give no indication of any qualitative change in the metabolism. The lowest average basal quotient is 0.75, and this is exactly what might be expected in patients with exceedingly high metabolism. In Case 1 (Max W.) the quotients rose to 0.94 on one day and 0.98 on another after the ingestion of 100 gm. of dextrose. The latter figure shows that 80 per cent of the calories was being derived from carbohydrate from two to three hours after the sugar was taken. The urine passed immediately afterward contained 3.9 gm. glucose, but it is evident that this glycosuria was not due to any impairment of the power to metabolize carbohydrates. The explanation must be sought in an abnormality of mobilization. Cramer and Krause<sup>27</sup> show that after the ingestion of thyroid substance the liver no longer retains glycogen as before.

#### DIRECT AND INDIRECT CALORIMETRY

One contribution to the science of metabolism which can be made only by a respiration calorimeter is a comparison of the direct and indirect calorimetry. The former method depends on the direct measurement of the heat of radiation, conduction and vaporization. The latter depends on the measurement of carbon dioxide and oxygen and the calculation of the foodstuffs metabolized each hour. It has been shown in the fourth paper of this series that the two methods agree within 0.17 per cent when normal controls are studied in periods lasting three hours or more. In the seventh paper it was shown that the method of direct calorimetry gave a total which was 2.2 per cent less than the indirect total in typhoid fever, and that the average divergence of the two methods in the individual experiments was 5 per cent. In the cases of hyperthyroidism here reported, the total number of calories measured is 8,052 according to the indirect method, and 7,823 according to the direct method, which is 2.9 per cent lower. The individual experiments show that the average divergence is  $\pm 4.1$  per cent. With the cretin Benny L., the direct calorimetry was 1.5 per cent higher than the indirect. When one considers the technical difficulty of making short respiration chamber experiments on sick patients, the close agreement of two absolutely independent methods is very

<sup>27</sup> Cramer and Krause. Proc. Roy. Soc. London, 1913, B, LXXXVI, 550.

striking. The fact that the direct calorimetry is slightly lower can be ascribed to technical errors in the direct method, which have been discussed in previous papers. It may be due to an unmeasured loss of heat to the bed and bed clothing or to an error in the measurement of the average temperature change of the body. The effect of these errors is minimized in long experiments such as are used in normal controls, but it is necessary to use short experiments with patients. The slight disagreement does not point to any disturbance of the intermediary metabolism. The law of the conservation of energy holds good in exophthalmic goiter.

#### WATER ELIMINATION THROUGH SKIN AND LUNGS

In the thirteenth paper of this series it was shown that under the atmospheric conditions prevailing in the calorimeter experiments, normal men eliminated on an average 284 gm. of water an hour through skin and lungs. Of the total calories produced, the average percentage dissipated through vaporization of water was 23.9. Few of the experiments showed a deviation of more than 10 per cent. from this mean.

In hyperthyroidism the heat production and water vaporization are both increased, and in Table 9 we see that they are increased in almost equal proportion. The average water elimination of the severe and moderately severe cases is 39.9 gm. per hour. On an average, 25.7 per cent. of the heat is dissipated through vaporization, or almost the same as in the normal controls. The percentage rise in water elimination through skin and lungs would seem to be a valuable guide as to the extent of the rise in total metabolism.

#### SPECIFIC DYNAMIC ACTION OF PROTEIN AND DEXTROSE

Owing to the variations in the basal metabolism of goiter patients, the results of this part of the investigation are not as clear cut as might be desired. In Table 10 the figures obtained on Max W. (Case 1), Edwin T. (Case 2) and the little cretin, Benny L. (Case 12) are given. It is difficult to select the proper basis of comparison for these three groups. Should we use the same actual amount of food, the same amount per kilogram, per square meter of body surface or per calories metabolized per hour? Should we compare the results in terms of percentage increase in metabolism or in the terms of extra calories? In the two exophthalmic goiter cases the protein meals produced almost exactly the same percentage rise as in the normal controls. With Max W. (Case 1) the metabolism was higher after the meal containing the protein in the form of casein and egg albumin than after the same amount of protein as found in beef. Edwin T. (Case 2) showed just the opposite, but the meat contained more

TABLE 9.—WATER FILTRATION OF GOLDEN POND, BOSTON, 1914

	Average Water Per Foot	Average Filtration Per Foot	Percentage of Filtration Per Foot
Case 1 (Max W.)			
Feb 10, 1914	2.1	34.4	2.1
Feb 11, 1914	2.1	34.4	2.1
Feb 12, 1914	2.1	34.4	2.1
Mar 1, 1914	2.1	34.4	2.1
Mar 2, 1914	2.1	34.4	2.1
Apr 1, 1914	2.1	34.4	2.1
Apr 2, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 2 (Edwin T.)			
Mar 1, 1914	2.1	34.4	2.1
Mar 2, 1914	2.1	34.4	2.1
Mar 3, 1914	2.1	34.4	2.1
Mar 4, 1914	2.1	34.4	2.1
Mar 5, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 3 (James Mel.)			
Mar 1, 1914	2.1	34.4	2.1
Mar 2, 1914	2.1	34.4	2.1
Mar 3, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 4 (Dr G. S. L.)			
Apr 1, 1914	2.1	34.4	2.1
Apr 2, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 5 (Peter N.), Apr 14, 1914			
	2.1	34.4	2.1
Case 6 (Anna K.)			
Apr 25, 1914	2.1	34.4	2.1
May 1, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 7 (Anna R.)			
May 10, 1914	2.1	34.4	2.1
May 20, 1914	2.1	34.4	2.1
May 28, 1914	2.1	34.4	2.1
May 14, 1914	2.1	34.4	2.1
Average	2.1	34.4	2.1
Case 8 (Sarah M.), Apr 29, 1914			
	2.1	34.4	2.1
Case 9 (Marion B.), Feb 5, 1914			
	2.1	34.4	2.1
Case 10 (Mrs L.), Apr. 20, 1914			
	2.1	34.4	2.1
Case 11 (Bessie H.)			
Apr 8, 1914	2.1	34.4	2.1
Apr 13, 1914	2.1	34.4	2.1
Apr 18, 1914	2.1	34.4	2.1
Case 12 (Benny L.)			
Apr 10, 1914	2.1	34.4	2.1
Apr 23, 1914	2.1	34.4	2.1
May 1, 1914	2.1	34.4	2.1
Averages Severe Cases—			
Case 1 (Max W.)	2.1	34.4	2.1
Case 3 (James Mel.)	2.1	34.4	2.1
Case 4 (Dr G. S. L.)	2.1	34.4	2.1
Case 6 (Anna K.)	2.1	34.4	2.1
Moderately Severe—			
Case 2 (Edwin T.)	2.1	34.4	2.1
Case 7 (Anna R.)	2.1	34.4	2.1
Average of six cases	2.1	34.4	2.1



nitrogen than the casein meal. Max W. (Case 1) showed a somewhat smaller percentage rise in metabolism than the normal controls after 100 gm. dextrose. The findings on the small cretin Benny L. (Case 12) are difficult to interpret on account of his low calorific output, but he seems to show results not far from the normal.

It appears that the specific dynamic action of protein and dextrose is approximately the same as in health. There is certainly no marked increase such as some writers\* have surmised, and there is no marked decrease such as is found in typhoid fever. There is little difference between protein in the form of meat and in the form of casein and egg albumin.

TABLE 10—SPECIFIC DYNAMIC ACTION OF FOODS IN HYPERTHYROIDISM

Subjects	Food	No. of Experiments	Average Gm. N. or Dext. in Food	Average Gm. N. or Dext. per kg. of Body Weight	Average Gm. N. or Dext. per Cal. per Hour	Average Per Cent Rise in Metab. above Subject's Basal
Two normal men	Protein meal	2	10.1	0.149	0.144	9.7
Case 1 (Max W.)	Casein and meat	2	8.9	0.146	0.082	9.7
Case 2 (Edw. T.)	Casein and meat	2	9.6	0.19	0.12	9.0
Case 12 (Benny L.)†	Protein meal	1	3.6	0.15	0.135	13.0
Three normal men	Glucose*	3	100.0	1.77	1.56	9.7
Case 1 (Max W.)		2	100.0	1.64	0.92	5.5
Case 12 (Benny L.)†		1	100.0	4.20	3.7	15.0
Case 12 (Benny L.)†		1	70.0	2.94	2.6	7.0

\* Subjects were given 115 gm. commercial glucose, which are equivalent to 100 gm. pure glucose.

† Cretin.

#### THE EFFECTS OF TREATMENT

Max W. (Case 1), after a stay of four months in various hospitals, was in the Bellevue metabolism ward for five days before the first determination of his basal metabolism. He received no treatment except good food, mental quiet and rest in bed with permission to get up and walk about for a few minutes at a time. In seventeen days the metabolism fell 12 per cent. After this he received the Beebe serum treatment with 1 gram of potassium iodid twice a day. In the next nineteen days the metabolism fell about 9.5 per cent, and the general condition improved correspondingly. Then while the treatment was being continued, the heat production rose almost to its level before the serum was begun. After one whole year of serum injections, during which time he was at home and at work, he returned

to the hospital with a metabolism 5 per cent lower than the day before treatment was begun. His mental irritability had lessened, his strength had increased, but his heart had developed fibrillation.

Edwin T. (Case 2) first took to bed when he was admitted to the metabolism ward. After a week of absolute rest in bed the first basal test was made. Three days later the metabolism was 13 per cent, and a week later 10 per cent lower without medication. Subsequently it rose to within 4 per cent of its original level under the influence of homesickness and some personal worries. He was given serum, but circumstances made it necessary to operate before a calorimeter test could be made. April 21, 23 and 29 all the thyroid arteries were ligated under painless local anesthesia. Twelve days after the last operation, his metabolism was 20 per cent higher than before. He looked worse, but said he felt stronger.

James McD. (Case 3) was in the hospital twelve days before his first basal test. Immediately after this he was put on the Forchheimer ergotin and guinn hydrobromate treatment. In nineteen days the metabolism fell 5 per cent. April 10, one artery was tied, May 2, an operation was interrupted by collapse on the part of the patient. Twelve days after this the metabolism was 6 per cent above the lowest point previously measured.

Anna K. (Case 6) was admitted to Bellevue April 27 and placed in the calorimeter the next day. On the 29th two thyroid arteries were ligated. Two weeks later the metabolism had fallen 17 per cent, which is about the decrease usually found during the first two weeks a patient is at rest in a hospital.

The basal metabolism of Anna R. (Case 7) was measured the third day she was in the hospital, May 12. On that afternoon, and May 16, the four thyroid arteries were tied. Four days later the metabolism was 15 per cent above its original point, and eight days later it had changed but little. One year later it was at its original level.

The thyroid extract called thyroid "residue" had but slight effect on the metabolism. With Dr. G. S. L. (Case 4), a severe case, the metabolism rose slightly, with Miss B. H. (Case 11) it fell.

#### OBSERVATIONS ON A CRETIN

The basal metabolism of Benny L. (Case 12) averaged about 20 per cent below the normal for adults according to his measured surface area. Children of his size average about 40 per cent above the adult figure. This increase seems to be due chiefly to the process of growth which is lacking in the 36-year-old cretin. Although Benny's heat production is about half as great as that of a normal child of his size, we cannot consider him more than 20 per cent below the normal for adults. The specific dynamic action of protein and carbohydrate, as we have said before, appears to be normal, but it is hard

TABLE II—CLINICAL—

Subject, Date Weight, Surface Area, I linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated Cal
Case 1 (Max W ) 2/16/14 61.76 Kg 1.72 Sq M	Prelim	11 10							
	1	12 10	56.19	4.73	0.757	46.2	0.515	114.64	108.69
	2	1 10	57.28	57.00	0.760	46.04	0.515	124.68 239.72	116.54
Max W 2/18/14 62.02 Kg 1.72 Sq M	Prelim	11 46							
	1	12 46	41.81	32.14	0.917	42.52	0.628	112.45	111.71
	2	1 46	21.12	21.72	0.915	42.45	0.628	109.25	118.12
	3	2 46	28.26	22.17	0.846	42.25	0.628	111.22 232.99	114.49
Max W 2/20/14 61.60 Kg 1.72 Sq M	Prelim	11 5							
	1	12 26	32.77	31.99	0.747	40.14	0.466	104.85	102.72
	2	1 26	37.19	34.28	0.757	41.75	0.466	114.24 219.09	105.67
Max W 2/21/14 62.26 Kg 1.73 Sq M	Prelim	10 45							
	1	11 45	43.56	36.23	0.857	40.68	0.456	100.82	112.67
	2	12 45	45.07	33.52	0.678	41.87	0.456	117.20 238.02	116.41
Max W 2/25/14 61.18 Kg 1.71 Sq M	Prelim	11 32							
	1	12 32	41.10	26.32	0.625	39.25	0.817	121.27	114.35
	2	1 32	43.87	37.00	0.839	41.29	0.817	126.06 247.33	123.58
Max W 2/27/14 60.86 Kg 1.70 Sq M	Prelim	11 18							
	1	12 18	35.58	33.13	0.781	41.05	0.650	109.55	112.07
	2	1 18	35.94	34.25	0.763	41.90	0.650	112.78 222.33	112.12
Max W 3/2/14 60.47 Kg 1.70 Sq M	Prelim	11 50							
	1	12 50	37.25	35.42	0.765	45.44	0.663	116.70	112.23
	2	1 50	38.75	32.28	0.873	46.48	0.663	109.25 225.95	112.08
Max W 3/4/14 60.02 Kg 1.70 Sq M	Prelim	10 52							
	1	11 52	31.79	30.79	0.751	39.10	0.550	101.10	105.05
	2	12 52	34.55	32.04	0.784	45.17	0.550	106.19 207.29	111.50
Max W 3/23/14 59.20 Kg 1.68 Sq M	Prelim	11 06							
	1	12 06	28.32	27.13	0.759	34.87	0.319	89.59	98.12
	2	1 06	29.31	27.63	0.771	34.44	0.319	91.46	97.22
	3	2 06	31.76	29.39	0.786	37.98	0.319	97.79 278.84	96.40

—CATHARTIC IN ACTION

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TABLE 11—

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Year	Population	Area	Population Density
1990	1,000,000	100,000	10
2000	1,500,000	150,000	10
2010	2,000,000	200,000	10

\* Protein = 56.0 gm (Nitro = 8.95 gm), Fat = 8.5 gm, Carbh = 47.1 gm, 8.55 to 9.32 a.m.

\* Protein = 56.0 gm (Nitro = 8.95 gm), Fat = 8.5 gm, Carbh = 47.1 gm, 8.55 to 9.32 a.m.

TABLE 11—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxide, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Idw T 3/22/15 19 17 Kg 1 468 Sq M	Prelim	11 07							
	1	12 07	25.50	23.71	0.791	25.07	0.315	78.50	82.01
	2	1 07	29.12	26.28	0.807	25.17	0.318	88.61	87.01
	3	2 07	30.48	28.79	0.775	42.45	0.318	91.78 261.89	92.51
Idw T 5/11/15 50.37 Kg 1 483 Sq M	Prelim	11 23							
	1	12 23	31.02	28.27	0.718	48.24	0.432	92.16	95.53
	2	1 3	33.75	31.47	0.712	50.87	0.452	115.11 211.27	107.61
Idw T 11/1/15 52.63 Kg 1 508 Sq M	Prelim	11 55							
	1	12 55	31.77	29.89	0.766	53.89	0.388	97.73	95.07
	2	1 35	33.17	30.60	0.789	51.38	0.388	101.89	95.48
Case 3 (Jns McI) 3/12/15 41.16 Kg 1 319 Sq M	Prelim	11 16							
	1	12 16	31.31	28.78	0.792	40.88	0.398	95.77	91.74
	2	1 16	30.02	29.06	0.761	45.31	0.398	98.57	96.66
	3	1 46	16.67	15.27	0.794	22.09	0.398	50.84 245.18	48.20
James McI 3/31/15 39.98 Kg 1 303 Sq M	Prelim	11 00							
	1	12 00	30.55	26.24	0.816	29.79	0.316	88.61	80.65
	2	1 00	31.49	28.62	0.800	23.28	0.316	95.60 184.21	86.04
James McI 5/14/15 45.29 Kg 1 371 Sq M	Prelim	11 12							
	1	12 12	32.14	31.01	0.782	55.70	0.301	101.91	96.97
	2	1 12	33.71	31.25	0.776	58.92	0.301	103.73 208.64	101.66
Case 4 (Dr G S L) 4/9/14 71.78 Kg 1 89 Sq M	Prelim	11 08							
	1	12 08	33.19	31.02	0.756	30.25	0.393	105.33	105.66
	2	1 08	33.30	30.88	0.781	30.23	0.393	102.62 207.95	102.22
Dr G S L 4/16/14 69.40 Kg 1 86 Sq M	Prelim	11 20							
	1	12 20	32.58	31.94	0.742	35.50	0.460	101.83	106.58
	2	1 20	34.95	33.05	0.769	38.16	0.460	109.29 214.12	102.25
Case 5 (Peter N) 4/14/15 63.44 Kg 1 795 Sq M	Prelim	11 23							
	1	12 23	22.85	20.32	0.818	28.42	0.375	67.89	77.85
	2	1 23	24.71	21.14	0.850	28.19	0.375	71.28 139.17	76.70

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Direct Calo- rimetry (R. C. & Temp.), Cal	Preval Temp., C	Ave. Pulse	Work Added, C	Non- protein R. Q.	Per Cent Calories from			Calorie per Hour		Remarks
					Pro- tein	Fat	Carbo- hyd	Per kg	Per Sq M (Meeh)	
	57.11									Basal
70.6	57.1	109		0.720	1	0		1.00	47.71	Sleeping, very quiet
80.0	57.1	108	10.0	0.81	10	61	0	1.70	74.4	Postlun quiet
97.71	57.1	112	10.0	0.772	10	50	20	1.72	77.1	Sleeping
244.7										
	7.2									Basal after hy- dration
97.8	7.2	111	10.0	0.772	12	60	10	1.71	77.51	Restless
108.76	7.24	117	10.0	0.683	10	80	0	2.10	18.60	Restless
202.76										
	57.16									Basal 6 mos af- ter hydration
90.41	7.0	95	10.0	0.750	10	60	24	1.5	57.5	Quiet, sleeping
100.0	7.15	107	10.0	0.750		6	56	1.94	78.0	Quiet, awake
	58.26									Basal
87.48	58.1	100	10.0	0.750	11	64	20	2.0	60.24	Quiet, reading
92.07	58.0	110	10.0	0.744	11	70	10	2.40	67.15	Quiet, reading
91.66	58.21	114	10.0	0.755	10	64	20	2.47	69.20	Fairly quiet
211.21										
	58.4									Basal after quinine and ergotin
82.62	58.60	90	10.0	0.851	9	46	45	2.22	61.54	Quiet reading
91.47	7.21	90	10.0	0.859	9	62	20	2.00	65.00	Reading 22 min., restless 28 min
177.09										
	57.20									Basal after hy- dration
89.64	57.02	111	10.0	0.726	5	75	7	2.2	68.61	Fairly quiet
101.86	7.04	119	7.0	0.770	8	72	20	2.20	67.81	Fairly quiet
191.50										
	56.57									Basal
101.54	56.56	98	24	0.751	10	76	14	1.47	49.51	Quiet
102.91	56.58	101	16	0.782	10	67	23	1.43	48.27	Quiet
207.45										
	56.88									Basal, at 9.35 9.50 a.m. 10 cc thyroid "resi- due"
101.60	56.80	97	29	0.733						
104.17	56.81	101	58	0.764	12	80	8	1.51	50.42	Fairly quiet
205.77					11	71	18	1.57	52.57	Restless
	57.27									Basal
73.79	57.15	71	6	0.820						
75.80	57.13	71	2	0.858	15	62	33	1.07	34.66	Very quiet
149.59					14	41	45	1.12	36.30	Very quiet



TABLE 11—

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TABLE 11—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Furni- shed Cal
Case 11 (Bessie H.) 4/8/14 17.06 kg 1.42 Sq. M	Prelim	11 40							
	1	12 40	19.05	17.02	0.815	26.67	0.170	57.12	62.51
	2	1 40	19.41	16.68	0.846	26.21	0.159	56.44 113.56	61.34
Bessie H. 4/13/14 48.15 kg 1.43 Sq. M	Prelim	11 27							
	1	12 27	15.42	16.22	0.826	20.31	0.125	54.63	56.23
	2	1 27	19.49	17.81	0.795	21.51	0.125	59.60 114.23	59.53
Bessie H. 4/15/14 46.62 kg 1.41 Sq. M	Prelim	11 05							
	1	12 05	17.53	15.11	0.826	22.12	0.217	51.02	52.61
	2	1 05	15.57	16.57	0.815	27.10	0.217	55.49 106.51	54.57
Case 12 (Benny L.) 4/10/14 22.60 kg 0.829 Sq. M	Prelim	11 40							
	1	12 40	10.23	7.67	0.974	10.40	0.263	26.10	31.35
	2	1 40	10.23	8.58	0.847	10.51	0.263	23.63 54.73	32.70
Benny L. 4/14/14 23.60 kg 0.84 Sq. M	Prelim	11 52							
	1	12 52	13.13	9.40	1.016	12.54	0.293	32.58	32.82
	2	1 52	12.51	9.24	1.003	12.29	0.293	31.97	33.39
	3	2 52	12.05	8.99	0.975	11.69	0.293	30.91 95.46	33.82
Benny L. 4/21/14 24.01 kg 0.847 Sq. M	Prelim	11 10							
	1	12 10	11.23	8.10	1.003	13.82	0.316	27.01	33.30
	2	1 10	11.02	8.90	0.890	13.47	0.316	30.13	32.12
	3	2 10	11.07	9.04	0.890	13.21	0.316	30.48	33.95
Benny L. 4/23/14 23.97 kg 0.847 Sq. M	Prelim	11 10							
		12 10	9.44	7.70	0.885	10.58	0.226	26.21	26.47
		1 10	9.20	7.83	0.855	11.21	0.226	26.25 52.46	28.57
Benny L. 4/27/14 23.86 kg 0.847 Sq. M	Prelim	11 20							
	1	12 20	10.47	7.94	0.959	14.30	0.208	27.36	27.15
	2	1 20	10.75	8.33	0.939	13.70	0.208	28.58	29.55
	3	2 20	11.01	8.38	0.955	13.29	0.208	28.88 84.82	29.25
Benny L. 5/1/14 23.03 kg 0.833 Sq. M	Prelim	11 10							
	1	12 10	10.86	10.05	0.785	11.67	0.236	33.22	31.09
	2	1 12	10.91	9.96	0.797	11.88	0.236	32.99 66.21	31.80

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to find the proper basis on which to compare it with results obtained on normal adults. The administration of thyroid extract raised the metabolism to normal in three and a half days, increased the pulse rate from about 80 to 95, and made the patient sick and miserable.

#### THE THERAPEUTIC APPLICATIONS

Mental and physical rest is the surest means of securing the drop in the metabolism which indicates a diminution in the pernicious activity of the thyroid. Psychotherapy is of some value, and this combined with rest may account entirely for the improvement following most of the so-called medical cures. Previous observers have found little or no reduction in the oxidative processes after treatment with "Radogen," the serum of thyroidectomized horses, and the Roentgen ray. To this list may be added from the present work thyroid "residue," the ergotin and quinin hydrobromate treatment, and Beebe's serum. These remedies, however, were tried on but one or two patients, and a more favorable report might have been justified if more cases had been tested. In the treatment of hyperthyroidism, calorimeters and other forms of respiratory apparatus seem to be therapeutic nihilists.

Some observers have found a prompt drop in the metabolism after a partial thyroidectomy. Ligation of the arteries usually causes a distinct rise in heat production which may last several weeks. This shows that following a ligation of the arteries the patients should be kept as quiet as possible and thyroid extract should on no account be given.

It is quite possible that the above mentioned therapeutic agents control some of the minor symptoms of the disease or render the major symptoms less apparent to the patient and his physician. We cannot consider the patient to be anywhere near a cure until the metabolism has approached the normal. We cannot consider a therapeutic agent to be curative unless it causes the metabolism to approach the normal more quickly than the tendency toward spontaneous improvement aided by mental and physical rest.

The need of large amounts of food by exophthalmic goiter patients is clearly shown. There is no indication against the use of fairly liberal amounts of protein, and there is no reason to prefer the proteins of vegetables and milk to those of meat. The number of calories required per day varies with the weight of the patient, the severity of the case and the degree of muscular activity. In general, it may be said that exophthalmic goiter patients need from one and one-half times to twice as much food as a normal person under similar conditions. Several of the patients studied produced over 100 calories an hour while at rest. Max W. (Case 1) and Edwin T. (Case 2) showed a slightly negative nitrogen balance when receiving 3,500 and

4,000 calories a day. Every effort should be made to give food of high caloric value in large amounts, or there will be losses of body fat and protein.

#### SUMMARY AND CONCLUSIONS

The metabolism in exophthalmic goiter has been studied for the first time in a respiration apparatus which is also a calorimeter. Thirty-seven observations were made on eleven patients with this disease, and six experiments were made on a cretin. With some of the patients the nitrogen balance was also studied.

The measurement of the heat production gives us the best index of the severity of the disease and of the effect of treatment. Very severe cases show an increase of 75 per cent or more above the normal average, severe cases 50 per cent or more, and moderately severe and mild cases less than 50 per cent, while a few mild and several atypical or cases in which operation has been performed may be within normal limits. In severe cases the warmth of skin and sweating can be accounted for entirely by the necessity for the increased elimination of heat. At least a part of the tachycardia is due to the increased metabolism, and perhaps it might be possible to reproduce the extreme tachycardia, the cardiac enlargement, emaciation and mental irritability if we were able to stimulate the metabolism of normal men for twenty-four hours a day over a period of months or years.

The specific dynamic action of protein and of glucose is within normal limits, and there is no consistent difference between the effects of protein in meat and an equal amount in milk and eggs. One patient was able to derive 89 per cent of his calories from carbohydrate in an experiment when he was showing an alimentary glycosuria. There is evidently no interference with the oxidation of carbohydrates.

The methods of direct and indirect calorimetry agree very closely when one considers the technical difficulties. The method of direct calorimetry gave results which were slightly lower than the indirect, the total difference being 2.9 per cent, and the average difference in the individual experiments being  $\pm 4.1$  per cent. This and the absence of abnormal respiratory quotients shows that the law of the conservation of energy holds good in exophthalmic goiter, and that there is no profound disturbance of the intermediary metabolism.

The average water elimination through skin and lungs in the severe and moderately severe cases of hyperthyroidism is 39.9 gm per hour. The increase above the normal is closely proportional to the increase in heat production, 25.7 per cent of the calories are dissipated through vaporization in goiter patients, whereas the mean normal is almost the same, 23.9 per cent.

The level of the heat production was used as an index of the effect of medical treatment. Rest in bed for a week or more caused a drop of more than 10 per cent. The effects of treatment with Beebe's serum, thyroid "residue" ergotin and quinin hydrobromate was less marked each being tested on one patient. Ligation of the thyroid arteries with three out of the four patients studied caused a distinct rise in metabolism, the duration of which was uncertain. There is as yet no proof that any conservative form of treatment causes a greater reduction of metabolism than mental and physical rest.

One small cretin 36 years old produced about half the calories eliminated by children of his size. As estimated by the surface area, his metabolism was about 20 per cent below the normal adult level. Three and a half days of treatment with thyroid extract raised his heat production to normal.

NOTE.—The work here reported was made possible by the cooperation of a number of associates who should receive credit for the major part of the work. The analyses of food, urine and feces were made by Mr Frank C Gephart, with the assistance of Mr R H Harries and Mr R C Stone. The electrical control of the calorimeter was in charge of Mr G F Soderstrom, and the residual air analyses and calculations were made by Dr A L Meyer and Mr Harries. The results were checked and tabulated by Miss Grace Sims and Mr Stone. Miss Estelle Magill and her assistants, Miss A Honold, Miss M M Fauquier and others were responsible for the weighing and preparation of the food, the care of the patients and the collection of specimens.

I wish to express my thanks to Dr John Rogers for providing most of the patients and for cooperating very actively in the work. I also wish to thank Dr S P Beebe for supervising the serum treatment and Dr G R Lockwood of the First Medical Division of Bellevue for permitting the use of material from his ward, and to Drs W H Brundage, T C Janeway and R J Shea, who also sent patients for treatment and observation.

# CLINICAL CALORIMETRY

## FIFTH LXXXI PAPER

### THE BASAL METABOLISM IN PERNICIOUS ANEMIA\*

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NEW YORK

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#### HISTORICAL

The view that a paucity of hemoglobin must seriously impair the oxidative processes of the body received dogmatic credence for many years. Although based on *a priori* considerations, it was apparently supported by animal experimentation, chiefly that of Bauer.<sup>1</sup> In Bauer's experiments the effect of hemorrhage is difficult of ascertainment. Food, fasting and the mechanical effect of blood loss are disturbing factors. The vomiting of Bauer's dog leads one to suspect that the animal was unfit for the purpose in hand.

At any rate, subsequent investigation on animals failed to substantiate any pronounced fall in the metabolic functions of the body in anemia. The observations of Finkler,<sup>2</sup> Lukjanow,<sup>3</sup> Pembrey<sup>4</sup> and

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1. Baur. Ueber die Zersetzungs Vorgänge im Thierkörper unter dem Einfluss von Blutenziehungen, *Ztschr. f. Biol.*, 1872, viii, 567.

2. Finkler. Ueber den Einfluss der Stromungsgewindigkeit und Menge des Blutes auf die tierische Verbrennung. *Arch. f. d. ges. Physiol.* (Pflüger's), 1875, x, 368.

3. Lukjanow. Ueber die Aufnahme von Sauerstoff bei erhöhtem Procentgehalt desselben in der Luft, *Ztschr. f. Phys. Chem.*, 1883, viii, 315.

4. Pembrey. Influence of Bleeding and Transfusion on Respiratory Exchange, *Jour. Physiol.*, 1895, xv, 449.



Gurber and Delchies effected a modification of the current hypothesis, inasmuch as no permanent departure from the normal metabolism could be found. There are variations, to be sure, but the tendency is distinctly toward normality. The slight increase in heat production which Fredericq<sup>5</sup> measured with the d'Arsonval compensation calorimeter is well within the limits of the experimental error. Only once did Hari,<sup>7</sup> working in Tanga's laboratory with a Rubner calorimeter, find an increase of 12 per cent in the heat production of a dog.

The anemias in animals have been artificially induced by blood-letting. It is open to question whether the anemias studied in animals are at all comparable with those obtaining in the clinic. When we come to the application of experimental methods to clinical anemia, the problem at once becomes decidedly more complicated. In addition to the simple anemias, there is the unique type of pernicious anemia. Chlorosis and leukemia may be included in the category because of their low hemoglobin content. Any difference that the clinical forms show may, quite apart from refinement of technique, be ascribed to essential differences between anemias artificially induced and anemias arising from pathologic agencies.

Magnus-Levy<sup>8</sup> points out that Pettenkofer and Voit's pioneer experiment on a leukemic man, if properly interpreted, actually reveals an increase in the metabolism.

Both Kraus<sup>9</sup> and Bohland<sup>10</sup> find the metabolism near the upper physiologic limits, and that in some cases (Bohland) it may really exceed these limits. Thiele and Nehring,<sup>11</sup> while observing a slight increase in secondary anemia, could not establish a diminution in the oxygen intake in chlorotics. In the hands of Magnus-Levy,<sup>12</sup> pernicious anemia yields a metabolism somewhat elevated. Grafe<sup>13</sup> finds

5 Gurber and Delchies. Einfluss des Aderlasses und der Transfusion auf den Wert des Atmungsstoffwechsels, Jahresb u d Fortschr d Thierchem (Maly's), 1906, p 561.

6 Fredericq. De l'action physiologique des soustractions sanguines, Jahresb u d Fortschr d Thierchem (Maly's), 1887, p 377.

7 Hari. Der Einfluss grosser Blutverluste auf die Kohlensäure- und Wasserausscheidung und Wärmeproduction, Arch f d ges Physiol (Pflüger's), 1909, pp 130, 187.

8 Magnus-Levy. Ueber den Stoffwechsel bei einem leukämischen Mannes, Ztschr f Biol, 1869, v, 319.

9 Kraus. Ueber den Einfluss von Krankheiten auf den respiratorischen Gaswechsel, Ztschr f klin Med, 1893, xxi, 458.

10 Bohland. Ueber den respiratorischen Gaswechsel bei verschiedenen Formen der Anämie, Berl klin Wchnschr, 1893, xvi, 417.

11 Thiele and Nehring. Gaswechsel bei anämischen Zuständen, Ztschr f klin Med, 1896, xxx, 41.

12 Magnus-Levy. Der Einfluss von Krankheiten auf den Energieshaushalt im Ruhestand, Ztschr f klin Med, 1906, lx, 179.

13 Grafe. Die Steigerung des Stoffwechsels bei chronischer Leukämie, Arch f klin Med, 1911, cii, 406.

an amazing augmentation in leukemia. The results of these observers will receive further consideration.

#### EXPERIMENTAL PROCEDURE

The six cases of anemia which we wish to present were all studied from sixteen to eighteen hours after the last meal. The patients were at rest and in the lying posture. They were allowed to turn in bed occasionally and move their arms a little. While it is desirable that there should be no unnecessary movements, we believe the subject should be as comfortable as the conditions of the experiment will permit.

The exact routine previous to the actual observation has received detailed consideration in another place<sup>14</sup>. The body temperature was measured by means of an electric resistance thermometer placed in the rectum. Surface thermometers were not used. It has been found that when there are no rapid fluctuations in body temperature the rectal temperature is the more reliable but is by no means absolutely satisfactory. Owing to the limitations of the rectal thermometer, and its failure to register accurately the mean temperature changes of the body, we still use the method of indirect calorimetry as a standard, for reasons previously discussed.

#### HISTORIES OF PATIENTS

**CASE 1—History**—Daniel V. (splenic anemia, congenital syphilis), aged 21 years, elevator boy, white, French West Indies, admitted April 16, 1913, discharged July 30, 1913. Had severe dysentery in 1897, and tropical fever with black stools in 1902. He had pain in the left side in 1910. He came to New York in 1912. A fine rash appeared on the body March 30, 1913, and the patient became pale. March 27 and again two weeks later, he vomited blood.

**Physical Examination**—April 16, the patient was tall and thin, with porcelain colored skin. Soft systolic murmur. Spleen palpable 7 cm. below costal margin. Hemoglobin, 25 per cent, erythrocytes, 1,700,000. Differential count normal except for 15 per cent myelocytes. Wassermann reaction positive. April 19, transfusion, 500 c.c. Spleen larger. April 23, transfusion, 750 c.c. April 24, spleen 11 cm. below costal margin in midclavicular line. Dark stools. April 26, transfusion, 760 c.c. Hemoglobin, 25 per cent, erythrocytes, 1,976,000. May 9, patient put in the calorimeter. Blood pressure systolic, 108, diastolic, 48, temperature 99-100, pulse 96, respiration 20, stools, four or five every day. Wassermann positive.

The spleen was removed several weeks later, and the patient improved rapidly. He was seen a year later in good health.

**CASE 2—History**—Andrew K.<sup>1</sup> (pernicious anemia), aged 27, plumber, entered the hospital Sept. 10, 1911, with a high grade of anemia. He improved

14 Gephart, F. C., and Du Bois, E. F. Clinical Calorimetry, Fourth Paper, The Determination of the Basal Metabolism of Normal Men and the Effect of Food, *THE ARCHIVES INT. MED.*, 1915, xv, 835.

15 Case reported by Coleman and Hartwell. *Med. Rec.*, New York, 1914 lxxxv, 1160.

under the syrup of ferrous iodid, sodium cacodylate and Bland's pills. He was discharged Nov. 1, 1911, and readmitted June 23, 1913. He worked as street car conductor but had to stop work because of weakness. There was no history of syphilis.

*Physical Examination*—The patient's skin was lemon yellow, there was extensive pigmentation, and the teeth were in bad condition. The spleen was three fingers' breadth below the costal margin. Jan. 24, 1913, the hemoglobin was 50 per cent, erythrocytes, 1,600,000, marked anisocytosis and poikilocytosis. Slight polychromatophilia. Leukocytes 6,000. Stools negative. During the ensuing four months there were low, continued fever attacks of diarrhea, progressive weakness and high pulse rate. Several transfusions were made. The last transfusion was interrupted by hemolysis. Two hours later severe chills and temperature of 103.8. Four hours later 2 ounces of bloody urine.

*Treatment and Course*—July 8, normoblasts 20 to every 100 leukocytes. Leukocytes, 2,000, polymorphonuclears 64 per cent, lymphocytes, 30 per cent, large mononuclears 3 per cent. October 29, splenectomy. Cytologic details essentially those of erythropoiesis and myelopoiesis. November 3, lemon yellow color disappeared. Picture of severe secondary anemia. November 17, leukocytes 12,000. December 6, leukocytes 16,000. December 29, hemoglobin, 27 per cent, erythrocytes 1,280,000, normoblasts 51, and megakaryoblasts 11 to every 200 leukocytes. Jan. 6, 1914, leukocytes 22,400, January 13, 29, neosalvarsan. Patient grew weaker. February 25, hemoglobin 18 per cent, erythrocytes 1,264,000. Normoblasts 111 and megakaryoblasts 16 to every 200 leukocytes. March 11 and 17, patient put in calorimeter. Pulse during March ranged from 109 to 124, respirations from 24 to 28, blood pressures, systolic, 142, diastolic 50 (March 27), temperature from 99 to 100. April 24, patient looked and felt better. Beginning to sit up. April 28, Wassermann reaction positive. Patient died December, 1915.

*Case 3—History*—Martin C. (pernicious anemia, transverse myelitis), driver, aged 32, admitted Jan. 8, 1915, died December, 1915, complained chiefly of weakness, shortness of breath, palpitation and paralysis of legs. In 1905 he slipped and had a bad fall which left him with a persistent pain between the shoulders. One year later the pains suddenly disappeared, but his legs began to grow numb and he lost good control of his feet. Soon after he was unable to walk and unable to control his bowels. In 1912 he began to grow stronger, and was able to walk with crutches. In February, 1914, he noticed general weakness. In December, a month before admission, he began to suffer from anemia, dyspnea, palpitation, nausea and insomnia.

*Physical Examination*—January 8, the patient was very pale, poorly developed and poorly nourished. Cardiac impulse forceful and diffuse. Apex in fifth space 5.6 cm, left border 12 cm from midsternal line, base in third space. Presystolic thrill over precordium. Presystolic murmur and systolic murmur at apex, the latter transmitted to axilla. Systolic murmur at aortic area. Corrigan pulse. Spleen palpable. Legs paralyzed, wasted and atrophic. Babinski reflex present. Lymph nodes generally enlarged. Incontinent of urine. January 13, eyegrounds showed presence of old retinal hemorrhages. January 20, erythrocytes, 650,000, normoblasts, 47, megaloblasts, 6. Anisocytosis, poikilocytosis and polychromatophilia marked. January 29, patient in the calorimeter. January 28 to February 23, temperature from 99 to 101, pulse from 100 to 124, respirations, from 20 to 30. February 2, hemoglobin 23.4 per cent. February 10, fluid on left side of chest. Thoracentesis. February 16, hemoglobin, 20 per cent. February 27, dullness on left side persisted. March 17, heart not enlarged. Systolic murmur over second left space and over apex. Edge of liver felt indistinctly at umbilicus. March 23, erythrocytes, 472,000, leukocytes 2,600, anisocytosis and poikilocytosis very marked. May 4, patient put in calorimeter. Hemoglobin, 21 per cent. Apex impulse diffuse. Left limit dul-

ness, fifth space 13 cm, fourth space, 11.8 cm, third space, 10 cm, right limit, 28 cm from midsternal line. Loud booming systolic murmur at apex. To left of sternum there was a soft blowing sound in diastole. Posteriorly left side flatness below angle of scapula. Patient later got up in a chair and dressed himself. Slightly jaundiced. April 24 to May 22, temperature normal to 100, pulse 72 to 115, respiration, 20 to 24. At necropsy in December, 1915, a bony tumor was found pressing on the spinal cord causing a transverse myelitis.

**CASE 4—History**—Bartolo D. (pernicious anemia), aged 50 laborer, admitted Feb. 22, 1915, discharged March 21, 1915 complained chiefly of weakness, and pain in abdomen. Four months ago he felt sick but was able to continue work.

**Physical Examination**—February 22 poorly nourished. Appearance chronically ill. Skin of peculiar greenish yellow. Conjunctiva pale. Heart regular in rate, force and rhythm. Soft systolic murmur over entire precordium. Pulse regular in rate, force and rhythm. Tension low. Vessel walls thickened. Slight distention of abdomen. Extremities wasted. General lymphatic enlargement. February 23, blood pressure 95 (systolic). February 24 temperature rose to 100.7 after which it remained below 100. Pulse varied from 80 to 100. February 28 blood pressure systolic 92, diastolic 70. March 4 stools negative. March 5 red cells 1,328,000, hemoglobin, 27 per cent, megaloblasts, 6, leukocytes 4200, polymorphonuclears, 71, lymphocytes 28. March 15, condition unchanged. Patient put in calorimeter. Complained of weakness and toothache. Stools large, possibly due to poor absorption. On strong positive nitrogen balance. March 18 red cells 2,200,000, hemoglobin, 44 per cent. Wassermann reaction negative.

**CASE 5—History**—Daniel O. (pernicious anemia, mitral stenosis and insufficiency), aged 38 steam fitter, admitted April 11, 1915, discharged May 10, 1915 complained chiefly of dizziness and weakness. Pain in lower lumbar region. The patient was moderately alcoholic. In 1905, kidney trouble. Had been able to work hard during past year. For several months had had a dry cough, slight impairment of vision. In March friends noticed pallor. April 4, 1915, pains in lower lumbar region with fainting and dizziness.

**Physical Examination**—April 11th, patient was pale and sallow. Looked sick. Conjunctiva edematous. Face puffy. Teeth bad. Lungs showed signs of chronic bronchitis and passive congestion, especially posteriorly. Sibilant and sonorous râles. Heart sounds of poor muscular quality. Presystolic thrill and systolic murmur over apex, the latter transmitted to the back. Aortic second somewhat accentuated. Pulse regular in rate and rhythm, and of fair force. Liver two finger' breadth below umbilicus. Spleen not felt, but area of dullness increased. April 15, red cells, 1,800,000, hemoglobin, 40 per cent, polymorphonuclears, 56, transitionals, 16, lymphocytes, 16, large mononuclears, 8, eosinophils, 25, mast cells, 15, megaloblasts, 2. Respirations, 20. April 26, patient put in calorimeter. Felt better than on admission. Not strong enough to work. Lemon tinted color. Eyelids puffy. Could walk up one flight of steps without stopping. May 4, blood pressure systolic, 130, diastolic, 80. May 10, no complaints. Discharged. (Urine showed faint trace albumin, occasional casts, and numerous leukocytes.)

#### DISCUSSIONS OF RESULTS

The average figures for the normal metabolism have been given in the thirteenth paper of this series.

In pernicious anemia we have obtained an increase of metabolism in all of the five cases. The figures vary from 2 to 33 per cent above the average normal. The highest heat production was found in

Martin C (Case 3) Unfortunately his temperature was a trifle above the normal, and he was also a little restless during this observation, as is indicated by the work-adder, the readings of which were 25, 22 and 31 for the first, second and third hours, respectively. A reading of 7 cm is equivalent to turning from back to side. A correction of at

TABLE 1—DETAILS OF—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen Gm	R:Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Case 1 (Daniel V ) 5 9/11 61 1/2 kg	Prelim	9 40							
	1	10 40	22 22	20 55	0 822	29 50	0 223	65 82	59 74
	2	11 40	24 08	22 18	0 784	31 20	0 223	70 71	63 02
	3	12 40	24 05	21 50	0 710	32 40	0 253	72 02	65 51
Case 2 (Andrew K ) 3 11/14 52 72 kg	Prelim	10 55							
	1	11 55	23 54	22 55	0 874	22 16	0 519	75 28	63 18
	2	12 55	25 45	21 01	0 845	22 25	0 519	73 47	72 61
Andrew K 3/27/14 52 03 kg	Prelim	10 45							
	1	11 45	23 55	20 60	0 831	28 54	0 507	69 21	73 40
	2	12 45	24 00	21 30	0 840	28 55	0 507	71 75	72 89
Case 3 (Martin C ) 1/29/15 47 80 kg 1 49 Sq M	Prelim								
	1	12 02	26 13	27 62	0 805	22 67	0 304	78 68	69 35
	2	1 02	24 04	22 06	0 772	27 44	0 560	74 49	76 01
	3	2 02	26 57	24 64	0 784	31 70	0 560	81 43	79 65
Martin C 5/4/15 44 21 kg 1 44 Sq M	Prelim								
	1	12 16	22 02	19 12	0 838	27 39	0 237	64 41	60 69
	2	1 16	20 68	16 87	0 891	25 61	0 237	57 53	55 93
Case 4 (Bart D ) 3/15/15 41 80 kg 1 39 Sq M	Prelim								
	1	12 18	16 28	13 76	0 861	16 01	0 224	46 55	52 47
	2	1 18	16 68	15 27	0 706	17 06	0 224	50 79	53 64
	3	2 18	17 65	15 41	0 833	16 65	0 224	51 84	51 28
Case 5 (Daniel O ) 4/26/15 60 05 kg 1 68 Sq M	Prelim								
	1	12 30	21 64	20 57	0 765	31 38	0 398	67 80	40 68
	2	1 30	22 80	21 55	0 769	31 30	0 398	71 06	46 89

least 10 per cent is therefore necessary to account for these two factors

Only in Cases 2 and 3 (Andrew K, and Martin C) did the heat production exceed the range of normal variation. Both are examples of severe anemia from the clinical point of view, with a hemoglobin

percentage of less than 25. It is of interest to note that Martin C had practically lost the use of his legs, and that his extremities were wasted and atrophic as the result of a transverse myelitis.

Bartolo D and Daniel O (Cases 4 and 5) cannot be said to show a pathologic increase of metabolism. It is not likely that the insuf-

## —CALORIMETRIC EXPERIMENTS

Direct Calorimetry (Rectal Temp.), Cal	Rectal Temp., C	Average Pulse	Work Added, Cal	Non-protein R Q	Per Cent Calories from			Calories per Hour		Remarks Surface Area Meeh's Formula
					Protein	Fat	Carbohydr	Per Kg	Per Sq M	
	37.10									Basal, Sq M = 1.915
65.42	37.22			0.524	12	5	83	1.12	35.94	Very quiet, slept most of time
67.77	37.30			0.757	12	64	24	1.20	38.49	Slightly restless
70.15	37.40			0.798	12	61	28	1.19	38.08	Restless
	37.13			.	.					Basal, Sq M = 1.731
67.18	37.23	102	14.7	0.842	15	44	38	1.47	43.55	
77.47	37.55	103	43.5	0.855	19	40	41	1.8	42.44	
	37.30	.		.						Basal, Sq M = 1.706
66.77	37.15	101	24.6	0.825	12	49	39	1.32	40.57	Asleep most of 1st period
72.55	37.15	95	41.0	0.845	11	47	42	1.38	42.06	Asleep half of 2d period, restless in sleep
	37.00									Basal, Sq M = 1.622
76.79	38.05	107	24.5	0.800	12.3	50.7	28.0	1.015	45.51	Somewhat restless
75.59	38.05	104	22.0	0.760	19.9	65.7	14.8	0.961	45.93	Restless 5 min
77.43	38.01	105	21.7	0.740	18.4	72.1	9.05	1.011	49.77	Restless 5 min
										Basal, Sq M = 1.539 (M)
59.25	36.60	91	24.0	0.811	9.4	49.1	41.2	1.301		Fairly quiet, voided
55.73	36.60	88	6.0	0.902	10.7	30.3	58.8	1.457		Very quiet
	37.24									Basal, Sq M = 1.483
52.24	37.24	71	7.0	0.869	12.7	38.6	48.7	1.114	31.39	Very quiet
50.94	37.23	67	12.0	0.793	11.7	53.1	25.2	1.215	34.25	Quiet
53.03	37.20	63	6.0	0.837	11.4	48.2	40.4	1.240	34.06	Quiet
										Basal
61.08	37.04	78	15.0	0.757	15.6	68.9	15.5	1.129	35.91	Quiet
62.64	37.00	76	16.0	0.763	14.8	69.5	15.7	1.183	37.64	Quiet

iciency of the mitral valve in Daniel O's case could in any way have affected his metabolism. Clinically the condition of these two patients was not so severe. Their hemoglobin approximated from 40 to 44 per cent of the normal. Daniel O was able to walk up one flight of steps without stopping on the day of the observation.

TABLE 2—SUMMARY OF CALORIMETER EXPERIMENTS, AVERAGES OF PERIODS, AND BASAL EXPERIMENTS ON MEN

Subject and Date	Weight, Kg	Age, Yrs	Aver Calories per Hour, Indirect	Aver age R Q	Indirect Calorimetry Average per Hour						Total Calories expended	Per Cent of Direct	Remarks		
					Aver age Calories per kg	Per Sq M For multi	Per Cent Direct from Average Normal Basal Met	Aver age Normal Basal Met	Per Sq M For multi	Per Cent Direct from Average Normal Basal Met				Per Sq M For multi	Per Cent Direct from Average Normal Basal Met
Case 1 (Daniel V) 5/9/13	61.35	21	71.81	0.803	1.17	37.70	1.5	217			2170	—	Slightly restless		
Case 2 (Andrew K) 3/11/14	52.72	27	71.12	0.879	1.41	42.79	2.4	217			1410	—2.5	Quite quiet		
3/27/14	52.03	27	70.49	0.855	1.5	41.11	1.9	217			1512	—1.3	Asleep		
Case 3 (Martin O) 1/29/15	47.80	32	78.50	0.787	1.66	46.21	4.01	17			160	—1	Slightly restless		
5/4/15	41.21	32	69.97	0.865	1.379	39.62	1.12	17	42.15		1114	—3	Quiet		
Case 4 (Bartolo D) 3/15/15	41.80	50	49.73	0.820	1.189	33.53	1.55	205	5.94		1015	—1.5	Quiet		
Case 5 (Daniel O) 4/26/15	60.03	38	69.43	0.767	1.156	26.73	1.60	17	10.0		155	—0.9	Quiet		
											1105	—1.7			

Daniel V (Case 1) is a case of splenic anemia with congenital syphilis. At present we do not know what bearing the history of syphilis has in this connection.

The literature affords considerable evidence that the methods of direct and indirect calorimetry may show remarkable agreement. This agreement has been shown by Rubner and Lusk on dogs, by Atwater and Benedict on man, by Carpenter and Murlin on parturient women, and by Howland on babies. Gephart and Du Bois,<sup>16</sup> in their study of normal men, found that the totals of indirect and direct heat production came within 0.17 per cent of each other, and that even in one hour periods the agreement was striking.

It is of the utmost importance to determine whether the same agreement can be demonstrated in disease. Coleman and Du Bois<sup>16</sup> in their series of sixty experiments on typhoid patients, obtained an average divergence in individual experiments of 5 per cent, and a total divergence of 2.2 per cent.

In our series of anemic patients (Table 2) the total divergence between direct and indirect calorimetry is about 3.3 per cent. In three of the observations the variation is from 1 to 3 per cent. The greatest discrepancy is 12 per cent. In hourly periods the least divergence is 1 per cent, the greatest 12 per cent. In the total there were seventeen one hour periods. In ten of these periods the two methods agreed within 2.5 per cent, in two, within 8 per cent, in four, within from 10 to 12 per cent.

The relationship between the volume of carbon dioxide produced and the volume of oxygen consumed justifies the inference that there is no profound qualitative change in the metabolism of pernicious anemia. There is no evidence of increased protein consumption. The nonprotein respiratory quotients vary from 0.76 to 0.87, indicating that fat and carbohydrate are burned to the same end-products as in health.

In Table 3 we have tabulated the results obtained by others in a variety of anemias. In all cases in which the heat production was not given, we have converted the oxygen consumption per kilogram per minute into calories per square meter per hour, on the assumption that 15 per cent of the calories are derived from protein. The area of body surface was computed according to Meeh's formula. We have indiscriminately applied the normal figure 34.7 calories per square meter per hour to all observations in arriving at the percentage increase or decrease in metabolism except in our own cases, in which the linear formula standards have been used in all cases measured by this method. The standard normal of 34.7 is not strictly accurate,

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16 Coleman, Warren, and Du Bois, E. F. Clinical Calorimetry, Seventh Paper, Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, *THE ARCHIVES INT. MED.*, 1915, xv, 887.



Observer	Disease	Patient	Sex	Age, years	Weight, kg	Temperature	Pulse	R <sub>sp</sub>	Hb per cent	R Q	Calories per Sq M per Hour (Meeh's Formula)	Per Cent Above or Below Normal	Remarks
Grafe, I	Lymph Leuk	T S 1a	♂	50	60.0	36.2	100	73		0.760	18.66	-5	Very dyspneic restless at times
Grafe, I	Lymph Leuk	T S 1b	♂	50	67.5	36.4	100	72		0.840	22.60	-9	
Grafe, I	Lymph Leuk	T S 1c	♂	50	68.5	36.5	90	74		0.831	18.66	-10	
Grafe, E	Lymph Leuk	G K 2	♂	36	77.0	36.2	80	72		0.881	26.75	-6	
Grafe, I	Lymph Leuk	G L 3a	♀	65	48.2	36.0	90	70		0.883	14.45	-28	Asleep most of the day
Grafe, I	Lymph Leuk	G L 3b	♀	65	48.0	36.2	85	71		0.880	16.62	-25	Asleep most of the day
Grafe, E	Lymph Leuk	M T 1	♂	49	63.5	37.2	82	72		0.871	16.64	-27	Restless now and then
Grafe, E	Lymph Leuk	M D 5	♂	76	65.8	36.6	85	—		0.867	19.53	-11	
Magnus Levy	Lymph Leuk	I	♂	69	57.5			—		0.788	14.13	-70	All observations
Grafe, E	Myel Leuk	F N 6	♀	72	64.3	37.6	82	70		0.787	20.29	-13	
Grafe, E	Myel Leuk	M H 7	♀	73	71.0	36.7	80	18		0.777	19.70	-13	
Grafe, I	Myel Leuk	H B 8	♂	48	77.5	37.5	80	18		0.814	18.11	-22	
Kraus, F	Spl Med Leuk	M B	♂	60	55.0	Normal	80	12	70	0.770	18.67	-10	
Kraus, F	Spl Med Leuk	M B	♂	60	75.0	Normal	80	12	70	0.772	16.15	-35	
Kraus, F	Spl Med Leuk	M B	♂	60	55.0	Normal	80	12	70	0.777	17.53	-27	
Kraus, F	Spl Med Leuk	W K	♂	77	71.7	Normal	100-105	14	60	0.811	17.40	-28	
Kraus, F	Spl Med Leuk	W K	♂	37	71.7	Normal	100-110	14	65	0.814	16.72	-7	
Kraus, F	Spl Med Leuk	W K	♂	37	71.7	Normal	100-110	14	60	0.805	16.37	-12	
Kraus, F	Splenic Leuk	S W	♀	34	61.0	Normal	80	14	65-70	0.866	19.74	-13	
Kraus, F	Splenic Leuk	S W	♀	71	61.0	Normal	80	12	65-70	0.898	19.17	-12	
Bohland	Splenic Leuk	H	♀	73	53.5	Normal	114-110	22-24	—	0.880	51.84	-10	6.20 N
Bohland	Splenic Leuk	H	♀	33	75.5	Normal	114	22-25	—	0.880	27.80	-10	6.15 N
Bohland	Splenic Leuk	H	♀	28	53.5	Normal	108	20-23	—	0.840	26.71	-13	6.15 N
Bohland	Splenic Leuk	H	♀	23	53.5	Normal	112-116	10-12	—	0.840	24.80	-18	10.60 N
Kraus, F	Chlorosis	V H	♀	20	49.0	Normal	78-84	16	65	0.710	11.17	-10	
Kraus, F	Chlorosis	V H	♀	20	49.0	Normal	78-84	15	65	0.775	11.80	-18	
Magnus Levy	Chlorosis	I G	♀	20	44.8					0.845	24.01	-0.2	13 observations

Magnus Levy	Chlorosis	M W	♀	18	53.5	Normal	50	12	85	0.704	70.63	+ 7	8 observations
Thiele and Nehrung	Chlorosis	R	♀	22	57.5	Normal	50	12	85	0.902	31.76	- 8	Chr otitis media
Thiele and Nehrung	Chlorosis	R	♀	22	57.5	Normal	50	12	85	0.905	31.21	- 10	Chr otitis media
Thiele and Nehrung	Chlorosis	R	♀	22	57.5	Normal	50	11	85	0.859	31.97	- 5	Chr otitis media
Thiele and Nehrung	Chlorosis	P	♀	18	58.5	Normal	90-100	15	55	0.925	27.69	- 10	
Thiele and Nehrung	Chlorosis	P	♀	18	58.5	Normal	90-100	18	55	0.940	27.89	- 10	
Thiele and Nehrung	Chlorosis	P	♀	18	58.5	Normal	90-100	24	55	0.904	29.61	- 17	Complicated toothache of
Thiele and Nehrung	Chlorosis	P	♀	18	58.5	Normal	90-100	24	55	0.779	29.63	- 15	Complicated toothache of
Thiele and Nehrung	Chlorosis	P	♀	18	59.0	Normal	90-100	20	55	0.825	25.54	- 17	
Thiele and Nehrung	Chlorosis	P	♀	18	59.0	Normal	90-100	20	55	0.909	29.63	- 16	
Thiele and Nehrung	Chlorosis	P	♀	33	61.0	Normal	88-100	13	25	0.752	10.73	+ 17	
Kraus, F	See anemia	L S	♂	33	61.0	Normal	88-100	14	25	0.763	29.48	+ 14	
Kraus, F	See anemia	L S	♂	33	61.0	Normal	88-100	14	25	0.766	13.69	+ 27	
Kraus, F	See anemia	L S	♂	33	61.0	Normal	88-100	14	25	0.900	23.77	- 3	2 observations
Magnus Levy	See anemia	G S	♀	20	63.4					0.779	27.27	+ 7	4 observations
Magnus Levy	See anemia	W R	♂	10	47.7					0.775	20.53	- 12	8 observations
Magnus Levy	See anemia	B L	♀	27	47.5	Normal	—	19	—	0.877	5.79	+ 3	Very anemic after hemorrhoid bleed ing, slept part of time
Thiele and Nehrung	See anemia	B	♀	—	47.5	Normal	—	15	—	0.850	24.23	- 0.5	Slept part of time
Thiele and Nehrung	See anemia	B	♀	—	47.5	Normal	—	17	—	0.944	26.41	- 5	
Kraus, F	Pernicious anemia	A D	♀	46	54.0	Normal	96-103	14	20	0.710	37.52	+ 8	
Kraus, F	Pernicious anemia	A D	♀	46	54.0	Normal	96-103	15	0	0.709	10.55	+ 17	
Magnus Levy	Pernicious anemia	M	♀	40	44.7					0.813	28.87	+ 12	6 observations
Magnus Levy	Pernicious anemia	W	♀	45	42.5					0.758	26.17	+ 1	1 observation
Authors	Pernicious anemia, splenic	1 (D V)	♂	21	61.55	37.25	96	20	25	0.803	17.70	+ 8	
Authors	Pernicious anemia	2 (A K)	♂	27	52.72	37.25	100-124	24-28	20	0.839	12.99	+ 24	
Authors	Pernicious anemia	2 (A K)	♂	27	52.03	37.20	100-124	24-28	20	0.835	41.44	+ 19	
Authors	Pernicious anemia	3 (M C)	♂	32	47.80	38.60	100-124	20-20	24	0.787	18.07	+ 11	
Authors	Pernicious anemia	3 (M C)	♂	32	44.21	36.60	72-115	20-21	21	0.865	29.61	+ 7	
Authors	Pernicious anemia	4 (B D)	♂	50	41.80	37.30	80-100	18-21	14	0.890	33.53	+ 2	
Authors	Pernicious anemia	5 (D O)	♂	28	60.05	37.02			10	0.767	26.78	+ 6	

inasmuch as many of the subjects were women. In sixty-eight women, Benedict, Emmes, Roth and Smith found the heat production to be 32.2 calories per square meter per hour, or 7 per cent lower than in men.

It will be observed that Magnus-Levy<sup>12</sup> and Kraus<sup>9</sup> found the metabolism in pernicious anemia from 4 to 17 per cent above the normal. The correction for sex would increase the percentage in the case of Magnus-Levy, but would leave it unaffected in the case of Kraus, because his subjects sat on a chair, a posture which sometimes raises the metabolism.

It is interesting to notice the striking contrast between the metabolism of pernicious anemia and that of leukemia. Both Bohland<sup>10</sup> and Kraus<sup>9</sup> were led to erroneous conclusions regarding the metabolism of leukemia. This is to be explained by the fact that Bohland allowed a variation of over 30 per cent from the average consumption of oxygen of a normal individual at rest. Kraus' upper physiologic limit of 5.75 cc oxygen per minute is rather high. If we interpret their results with reference to the modern base line in terms of heat units, their leukemic patients show a marked rise of metabolism. Bohland, who used the Zuntz-Geppert apparatus, states that all of his experiments were performed from five to six hours after the midday meal, or from three to four hours after breakfast, or else in the morning in a "nuchtern" state. Three of the observations which we have tabulated came between 6 and 7 in the evening and one at 10 o'clock in the morning, so that in all four the metabolism was still affected by the previous ingestion of food. Kraus, who also employed the Zuntz-Geppert method, allowed his patients to sit upright on a chair. This in itself would doubtless elevate the metabolism somewhat.

Grafe<sup>13</sup> used a modified form of the Jaquet apparatus in his experiments on leukemic patients. Eliminating those experiments, in which the subject was dyspneic and very restless, we obtain figures from 6 to 50 per cent above the normal of 34.7.

Kraus,<sup>9</sup> Magnus-Levy<sup>12</sup> and Thiele and Nehring<sup>11</sup> have investigated chlorosis and secondary anemia. When we express the oxygen absorption which Kraus found in chlorosis, and secondary anemia in terms of calories, the metabolism is abnormally high. We must again remember that Kraus permitted his patients to sit during the observation. Magnus-Levy's results do not exceed the normal bounds. In the work of Thiele and Nehring we meet for the first time a lowered metabolism in an anemic state, although they, themselves, believed that a diminution in the oxygen intake could not be demonstrated in chlorosis.

## COMPENSATORY FACTORS IN ANEMIA

It is clear from the foregoing experimental results that a reduction in the hemoglobin does not preclude the possibility of either a normal or an augmented metabolism. There is no evidence that metabolism runs its course on a lower plane in anemia. The demand for oxygen may far exceed the demand in health. How, then, is the requirement met?

In health, oxygen combines with hemoglobin by reason of chemical affinity. It is conceivable that in disease Nature may resort to physical means of increasing the combining capacity of hemoglobin. Such a conception, however, appears improbable from a comparison of Butterfield's<sup>17</sup> work with that of Peters.<sup>18</sup> Butterfield found that the ratio of CO (or O<sub>2</sub>) : Fe averaged 399 in eleven patients, some of whom were anemic. This agrees remarkably well with the average specific oxygen capacity of 411, which Peters obtained with normal blood, using quite a different method. We may conclude that in anemia, physical means play no rôle in the absorption of oxygen apart from the slight amount taken up by the plasma in physical solution.

Normally the supply of oxygen to the tissues is beyond the immediate requirement. In anemia when the hemoglobin content is low and the volume per cent of oxygen is correspondingly diminished, the consumption of oxygen remains normal, or may even be above the normal. Since no means of augmenting the oxygen carrying capacity per unit of blood has been demonstrated, it is manifest that the margin of safety must be encroached upon and that the blood must return to the heart in various degrees of asphyxia. That this is actually the case appears in the work of Mohr,<sup>19</sup> Morawitz and Rohmer<sup>20</sup> and Kraus and Chovstek.<sup>21</sup> In certain forms of anemia, under conditions of rest and with a metabolism near normal, the extra quota of oxygen which Nature has generously provided would suffice. A simple calculation, however, will show that in some patients other factors must be brought into play. Let us take, for instance, the case of Andrew K. (Case 2), whose metabolism was high and whose hemoglobin was 20 per cent of the normal. With this amount of hemoglobin, 100 c c

17 Butterfield Ueber die Lichtextinktion, das Gasbindungsvermögen und den Eisengehalt des menschlichen Blutfarbstoffes in normalen und krankhaften Zuständen, *Ztschr f physiol Chem*, 1909, lxii, 173

18 Peters Chemical Nature of Specific Oxygen Capacity in Hemoglobin, *Jour Physiol*, 1912, xlv, 131

19 Mohr Ueber regulierende und compensirende Vorgänge im Stoffwechsel der Anämischen, *Ztschr f exper Path u Therap*, 1906, ii, 435

20 Morawitz and Rohmer Ueber die Sauerstoffversorgung bei Anämien, *Deutsch Arch f klin Med*, 1908, xciv, 529

21 Kraus and Chovstek Ueber den Einfluss von Krankheiten auf den respiratorischen Gaswechsel, *Ztschr f klin Med*, 1893, xxii, 573

of blood would contain 37 cc. of oxygen. Assuming a pulse rate of 70 and an average normal output per beat of 50 cc., the minute output of oxygen would be 130 cc. His actual need was about twice this, namely, 252 cc. oxygen per minute as determined by the calorimeter. His pulse rate averaged 101, and therefore his output per beat must have been at least 60 cc. to supply enough oxygen to meet the demands calculated according to the formula: Pulse Rate  $\times$  Output per beat per cent  $O_2 = 252$ .

Plesch<sup>22</sup> and Mohr<sup>23</sup> call attention to the increased output and pulse frequency in anemia. A more liberal supply of blood to the tissues may at times be favored by a greater respiratory volume. That the depth of respirations increase has been noticed by Jurgensen,<sup>24</sup> Kraus<sup>25</sup> and others. It is chiefly of value in facilitating the filling of the right heart. Its effect on the absorption of oxygen is negligible.

#### THE CAUSE OF HIGH METABOLISM IN ANEMIA

In anemia we frequently encounter signs of rapid regeneration. Normoblasts and megaloblasts may be present in secondary anemia, but are especially characteristic of pernicious anemia. Whether or not this is a reversion to the embryonic type of cell formation, the fact remains that these cells constitute a considerable mass of young tissue in the process of development. Their number in the peripheral blood is no measure of those present in the body. In the blood of rabbits with subchronic anemia experimentally induced there is a pronounced consumption of oxygen and production of carbon dioxide in vitro. This Morawitz<sup>24</sup> attributes to the presence of nucleated red cells.

In the leukemias we also see nucleated red cells, but their number is insignificant compared with the enormous increase in the white cells. Grafe<sup>13</sup> believes that the white blood cells are an important factor in the extra heat production of leukemia.

Zuntz, Lowy, Muller and Caspari<sup>25</sup> show that muscles poorly supplied with oxygen are functionally less efficient. Accessory muscles are called on to cooperate in the accomplishment of any task. The mechanism of the vital function of respiration and circulation becomes more complex. Proper breathing requires the activity of muscles that

<sup>22</sup> Plesch. Haemodynaemische Studien, Ztschr. f. exper. Path. u. Therap., 1909, vi, 526.

<sup>23</sup> Jurgensen. In von Noorden's Pathologie der Stoffwechsel, Ed. 1, 1893, p. 335.

<sup>24</sup> Morawitz. Ueber Oxydationsprozesse im Blut, Arch. f. exper. Path. u. Pharmakol., 1909, ix, 298.

<sup>25</sup> Zuntz, Lowy, Muller and Caspari. Hohenklina und Bergwanderungen, Berlin, 1906, Table XII, p. 435.

ordinarily play no rôle in respiration. Again, the respiratory muscles may serve in securing a more efficient circulation. In general, activity implies unusual effort, and hence the demand for additional oxygen.

#### CONCLUSIONS

Three mild cases of pernicious anemia showed very slight increase in the metabolism. In two severe cases the demand for oxygen was from 7 to 33 per cent above the normal average.

The basal metabolism of pernicious anemia is lower than that of leukemia, but, as a rule, higher than that of secondary anemia.

The agreement between the direct and indirect calorimetry as well as the respiratory quotients indicates that the basal metabolism of pernicious anemia is qualitatively identical with the normal.

Although the demand for oxygen may be increased, the compensatory processes in uncomplicated cases of pernicious anemia are capable of meeting the demand in spite of a greatly diminished hemoglobin content.

There is some ground for the belief that the height of metabolism is a measure of the severity of the clinical pictures.

# CLINICAL CALORIMETRY

## SIXTEENTH PAPER

### THE BASAL METABOLISM OF PATIENTS WITH CARDIAC AND RENAL DISEASE \*

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The literature contains extremely few reports of observations on the metabolism of patients with heart disease. The work most frequently referred to is a monograph of Kraus<sup>1</sup>. This study of the effect of fatigue in various pathologic conditions contains observations on the gaseous metabolism of three cardiac patients while at rest and while working on an ergograph, together with analyses of the oxygen and carbon dioxide content of the venous blood in seven cases. The metabolism experiments were made with the Zuntz apparatus. One of the most striking results is the extraordinarily low value obtained in all cases for the respiratory quotient. In the two milder cases the quotients for experiments with the subjects at rest and fasting were 0.743 and 0.603, while three similar observations in the more severe case gave as respiratory quotients 0.574, 0.534 and 0.614. Exercise brought about a rise of the quotient. In the last case exhausting work raised the quotient to 0.933 and 0.923. The blood-gas analyses showed an increase over the normal carbon dioxide content of the venous blood both at rest and during work. Kraus believed that the low respiratory quotients and the high blood carbon dioxide were best explained by assuming that one of the essential factors of the dyspnea of cardiac patients is that the lung has lost its ability to excrete carbon dioxide and take up oxygen normally, either on account of a disturbance of its glandular function (Bohr), or because of pathologic changes in the lining epithelium or the pulmonary vessels.

Grafe<sup>2</sup> reports observations made with the "Kopfrepirationsapparat" on the metabolism of seven patients with cardiac disease. The

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1 Kraus. Die Ermüdung als ein Mass der Constitution, Bibliotheca Medica, Abt. D<sup>1</sup>, Hefte 3, Cassel, T. G. Fisher & Co., 1897.

2 Grafe. Gaswechseluntersuchungen bei fortgeschrittenen Erkrankungen der Lungen an den Zirkulationsorganen, Deutsch. Arch. f. Klin. Med., 1909, xcv, 543.

method is open to criticism. The respiratory quotient was 0.885 in a case of congenital heart disease, 0.733 in one with Pick's cirrhosis, and 0.764 in a case of arteriosclerosis with myocarditis, but in the four other cardiac patients the quotients were remarkably low: 0.638, 0.632, 0.619 and 0.586. These instances with low respiratory quotients showed comparatively normal oxygen consumption, but low carbon dioxide production. Grafe demonstrates by calculations that it is quite impossible to accept the theory of Kraus, which accounts for the low quotients on the basis of carbon dioxide retention, as the amounts of carbon dioxide stored up in the body would be too enormous. He believes that the low respiratory quotients signify a qualitatively altered metabolism with incomplete oxidations, and suggests that the accumulation of carbon dioxide, which Kraus demonstrated by blood-gas analysis, may have injured the body protoplasm so that the chemical changes pursue an abnormal course. There seemed to be no relation between respiratory rate and increase of oxygen consumption.

While some of the respiratory quotients obtained by Grafe are so low that it is almost impossible not to suspect their accuracy, nevertheless his theory as to an altered metabolism finds some confirmation in the work of other authors who have shown that acidosis is frequently associated with cardiac disease. Thus, according to Beddard and Pembrey,<sup>3</sup> the alveolar carbon dioxide tension is very low in cases of decompensated cardiac disease. French, Pembrey and Ryffel<sup>4</sup> found it low in cases of congenital heart disease with cyanosis. Fitzgerald<sup>5</sup> obtained normal values for the alveolar carbon dioxide in the majority of cardiac cases, but low values in a case of mitral stenosis and extremely low figures in a case of congenital heart disease. Porges, Lemdorfer and Markovici<sup>6</sup> studied a considerable series of patients with heart disease, and found that in general the carbon dioxide tension of the alveolar air is normal in those which were without dyspnea, but that it tended to be below normal in the dyspneic patients. The lowest tensions in compensated patients without dyspnea occurred in two cases of congenital heart disease, both of which probably had open ductus Botalli. Lewis<sup>7</sup> and his associates have shown by investigations on the blood and alveolar air that the attacks of dyspnea so commonly seen in elderly patients with renal disease or advanced arteriosclerosis are accompanied by an acidosis which they believe to be the cause of the disturbance of respiration. In cases of pure valvular

3 Beddard and Pembrey. *Brit. Med. Jour.*, 1908, ii, 580.

4 French, Pembrey and Ryffel. *Jour. Physiol.*, 1909, xlix, Proc., p. 9.

5 Fitzgerald. *Jour. Path. and Bacteriol.*, 1910, xiv, 328.

6 Porges, Lemdorfer and Markovici. *Ztschr. f. klin. Med.*, 1913, lxxvii, 446.

7 Lewis, Ryffel, Wolf, Cotton and Barcroft. *Heart*, 1913, v, 45. Lewis and Barcroft. *Quart. Jour. Med.*, 1915, vii, 97.



disease with cyanosis, they found no evidence of acidosis, but that there may be an acidosis in severely decompensated cases, which disappears as compensation is regained, is shown by the observations of Porges, Lemdorfer and Markovici.<sup>8</sup> It is, however, particularly in the type of case which may be conveniently grouped under the heading of "cardiorenal" disease that the factor of acidosis assumes a more permanent and thus a more important part. The association of acidosis with chronic nephritis has been carefully discussed by Sellards<sup>9</sup> and by Palmer,<sup>10</sup> and its relation to the course of the disease has been studied by Peabody.<sup>10</sup> The significance of acidosis in investigations on metabolism was first suggested by Benedict and Joslin,<sup>11</sup> who showed that in two normal subjects an acidosis resulting from the administration of a carbohydrate-free diet was accompanied by an increase in the total metabolism. This observation has since been confirmed by Higgins, Fitz and Peabody.<sup>12</sup> Lusk believes that this increase is due to the increased protein metabolism of the carbohydrate-free periods.

#### METHODS USED

It is thus quite evident that in studying the metabolism of patients with heart disease it is of the utmost importance to know whether or not there is an acidosis. On account of its direct bearing on the subject of acidosis, and also on account of any other possible, but as yet unknown effects which a nephritis may exert on the metabolism, it is also of importance to know as much as possible about the functional capacity of the kidneys. At the time when the earlier of the cases reported here were investigated, renal function tests were not in general use, but the later cases were, whenever possible, studied with these points in mind. As an index of acidosis, the carbon dioxide tension of the alveolar air was determined. This was done by the Higgins modification of the method of Plesch, which has proved very satisfactory for clinical work. The normal alveolar carbon dioxide tension by this method is approximately 40 to 45 mm. In some instances the alkali tolerance test of Sellards<sup>9</sup> was used. The determination of the part played by the kidneys in cases of cardiac or cardiorenal disease is, of course, proverbially difficult and unsatisfactory. In general we have relied on the history, physical examination, urine examination, blood

8 Sellards. Johns Hopkins Hosp. Bull., 1912, xxiii, 289, *ibid.*, 1914, xxv, 141.

9 Palmer. Med. Communicat., Mass. Med. Soc., 1913, xxiv, 133.

10 Peabody, F. W. Studies on Acidosis and Dyspnea in Renal and Cardiac Disease, *THE ARCHIVES INT. MED.*, 1914, xiv, 236, Clinical Studies on the Respiration, II, The Acidosis of Chronic Nephritis, *ibid.*, 1915, xvi, 955.

11 Benedict and Joslin. Publications of the Carnegie Institution of Washington, 1912, Pub. 176.

12 Higgins, Fitz and Peabody. Unpublished.

pressure and phenolsulphonephthalein test to aid us in differentiating the pure cardiac from the renal or cardiorenal cases

The patients were all from the medical wards of Bellevue Hospital, but during the period of study they were kept in the special metabolism ward. The general method of conducting the observations was similar to that described in the third and fourth paper of this series.<sup>13</sup> The patients were usually put into the calorimeter for a short period in the afternoon, in order that they might become accustomed to the new surroundings, and then put in again for the actual experiment on the following day. As one of the chief points which we wished to investigate was the influence of dyspnea on the metabolism, quite a number of the decompensated patients were put into the calorimeter. In spite of their comparatively serious condition, however, no patient was in any way injured by his stay in it. The majority said they felt better when they came out, and, indeed, the period of absolute quiet seemed to have only a beneficial effect. The construction of the chamber described in the eleventh paper made it possible to study the metabolism of patients with orthopnea. The respirations were counted by watching the patient through the glass window in the side of the calorimeter, but the graphic records registered by the spirometer on a kymograph for the five minutes at the end of each period were of help, particularly in drawing attention to periodic breathing.

#### DISCUSSION OF RESULTS

The total number of patients investigated was sixteen. One of these (Case 3, Fred D) was examined first when he was decompensated and dyspneic (3a), and later when he was compensated (3b). Six cases (11, William S, 12, George M, 13, Marcus R, 14, David K, 15, William A, 16, Theodore S) were studied for purposes not directly connected with the present investigations so that the details on them are not complete, but they are included since they serve as controls of the more severely ill patients, and contribute information about various special points. Seven cases 2, Armon W, 3, Fred D, 4, Edward M, 9, Burrell P, 11, William S, 15, William A, 16, Theodore S) were instances of pure cardiac disease, two were cases of nephritis (12, George M, 14, David K) and six (1, Arthur V, 5, Charles L, 7, Edward W, 8, Henry R, 10, August F, 13, Marcus R) were mixed cases belonging to the "cardiorenal disease" group. At the time when they were in the calorimeter, five patients (1, Arthur V, 3a, F M, 10, August F) had moderately (2, Armon W, 5,

Case No and Name	Date	Age	Sex*	Indirect Calorimetry			Average per Hour		Average Normal Basal Calories per Sq M per Hour		Remarks
				Average Calories per kg	Per Sq M, Meeh	Per Cent Divergence from Average Normal Basal, Meeh	Per Sq M, Inear For mul's	Per Cent Divergence from Average Normal Inear	Accord Ink to Meeh's Formula	Accord Ink to Inear's Formula	
1 Arthur V	2/12/15	40	♂	157	514	+12	87	+18	17	97	Restless
2 Armon W	2/13/15	33	♂	121	386	+11	677	+19	217	97	Quiet
3 Fred D	2/15/15 2/23/15	17	♂	151 141	451 385	-17 0	58 127	+23 42	27 27	120 120	Very quiet Very quiet
4 Edward M	2/17/15	37	♂	118	395	+15			17		Restless
5 Charles L	2/19/15	51	♂	108	387	+26			35		Quiet
6 Anne T	2/20/15	14	♀	175	422	+10 ( )	150	-5 (f)	25 ( )	94 ( )	Slightly restless
7 Edward W	2/24/15	37	♂	168	518	+10			47		Slightly restless
8 Henry R†	2/26/15	40	♂	165	390	+4	4574	+14	17	17	Quiet
9 Burrell P	3/24/15	41	♂	129	373	+7	181	12	17	17	Restless
10 August F	5/1/15	62	♂	101	317	+3	399	5	35	22	Quiet
11 William S	2/10/15	48	♂	169	348	-2	417	5	17	97	Extremely quiet
12 George M	4/7/12 1/11/13 3/24/14 4/4/14	50	♂	168 101 163 163	331 317 311 310	+5 1 11 11			38 15 38 38		Restless Quiet Quiet
13 Marcus R	1/9/13	51	♂	134	435	+11			35		Very quiet
14 David K	3/21/13 3/24/13	51	♂	122 111	293 570	+5 159			35		Restless
15 William A	1/25/15 1/27/15	24	♂	113 117	67 579	+5 +9	26 412	0 4	17 17		Extremely quiet
16 Theodore S	1/28/11 1/30/11 2/5/14 2/9/14 2/13/14	32	♂	117 110 115 103 113	571 448 67 330 364	+9 +2 +7 -1 +7	451 37 39 71 411	+4 -2 -4 -7 -3	47 47 47 47 47		Very quiet Very quiet Very quiet Very quiet Very quiet

\* In this column, ♂ denotes male, and ♀ female

† In Case 8 (Henry R) there was some error in the measurements of the height or of the surface. The three measurements of the linear formula 1, 0 and 16 added together give a total length of 150 cm from soles of feet to suprasternal notch. His height was recorded as 153 cm. According to the linear formula measurement, his surface area was 1978 sq m or only 11 per cent below the figure of 2210 obtained by Meeh's formula. With 160 individuals of his body shape the true surface is usually about 20 per cent below the estimate according to Meeh. This would make his surface about 172 sq m. According to new height weight chart it would be 171. His metabolism per square meter per hour on this new basis would be about 15 per cent above the average, or 4570 calories per square meter.

Charles L. , 6, Annie T. , 7, Edward W. , 9, Burrell P. , 11, William S. , 13, Marcus R. ), and five had normal respiration (3b, Fred D. , 12, George M. , 14, David K. , 15, William A. , 16, Theodore S. )

*Respiratory Quotients*—In striking contrast to the results of Kraus and Grafe, which have been described above, all of the respiratory quotients in this series of cases fell within comparatively normal limits. Our lowest quotient was 0.73 (Case 4, Edward M. ). Of the ten cases reported by Kraus and Grafe, only four had respiratory quotients equal or above our lowest figure, while in the other six the results had to be explained as being caused by a qualitative alteration in metabolism. On the basis of the respiratory quotients, as obtained by us, there is no need to assume any change in the type of metabolism from the normal. In general there is a distinct tendency for the lowest quotients to be found in the cases with most dyspnea. Five patients, classed as having moderately severe dyspnea, gave as quotients 0.74, 0.75, 0.73, 0.75 and 0.82. In seven patients with slight dyspnea the quotients were 0.79, 0.76, 0.81, 0.79, 0.84, 0.82 and 0.78, while the patients without dyspnea showed the following quotients 0.88, from 0.80 to 0.83, from 0.74 to 0.75, from 0.81 to 0.85 and from 0.80 to 0.85 (Table 2)

#### DIRECT AND INDIRECT CALORIMETRY

In the previous papers of this series the close agreement between the methods of direct and indirect calorimetry with normal subjects has been demonstrated. In disease, owing to certain technical difficulties, there is a tendency for the method of direct calorimetry to average from 1 to 2 per cent lower, particularly if short periods are used. In the group of cardiac and nephritic patients here presented, the total of the calories measured by indirect calorimetry is 4,297.67, by direct calorimetry 4,214.53, or 1.93 per cent lower. This is remarkably good agreement, considering the technical difficulties, and indicates that there is no profound change in the metabolism which would upset calculations based on the method of indirect calorimetry.

#### TOTAL METABOLISM

The total metabolism is compared with the normal in terms of the heat production per square meter of surface area per hour. After the linear formula was devised, it was possible to measure most of the patients in this manner and use the results as a basis of the calculations. In all other cases it has been necessary to use Meeh's formula, which is fairly satisfactory with these subjects, since they all happened to be of about the normal body shape.

Of the five patients with moderately severe dyspnea, all but one (Case 10, August F. ) showed a distinct increase in metabolism. Of

TABLE 2—CLINICAL FINDINGS AND—

Case No. and Name	Age	Date in California	Diagnosis	Blood Pressure	Pulse Rate	Phthalein Per Cent
1 Arthur V	40	2/12/15	Chronic nephritis, chronic myocarditis with decompensation	110-70	60	2/17=22% 2/27=35%
2 Armon W	53	2/13/15	Double mitral disease, auricular fibrillation	110-70	77	—
3a Fred D	17	2/14/15	Double mitral disease decompensation	—	105	—
b Fred D		2/27/15	Compensated	95-70	86	—
4 Edward M	57	2/17/15	Mitral insufficiency, auricular fibrillation, decompensation	120-85	78	—
5 Charles L	24	2/19/15	Aortic and mitral insufficiency, chronic nephritis emphysema	150-60	71	50%
6 Annie T	14	2/20/15	Congenital heart disease, open ventricular septum, dextrocardia	95	102	—
7 Edward W	57	2/24/15	Chronic nephritis, cardiac dilatation, syphilis	100-100	112	10%
8 Henry R	40	2/26/15	Chronic myocarditis, emphysema, chronic nephritis	160-120	116	45%
9 Burrell P	41	3/24/15	Aortic stenosis and insufficiency mitral and tricuspid insufficiency, aneurysm of aorta	—	66	—
10 August F	62	5/1/15	Chronic nephritis, auricular fibrillation	170-110(?)	77	24%
11 William S	48	2/10/15	Adherent pericardium	110-80(?)	91	—
12 George M	56	4/7/15 4/14/15 3/24/14 4/4/14	Chronic nephritis, cardiac hypertrophy	170-95 170-55 105-115 160-102	64 59 60	
13 Marcus R	57	1/9/13	Chronic nephritis, mitral insufficiency, arteriosclerosis	90-160	81	
14 David K	54	3/21/13 3/24/13	Chronic nephritis, arteriosclerosis, inguinal hernia	105-110		
15 William A	24	1/25/15 1/27/15	Aortic insufficiency	140	61 66	
16 Theodore S	32	1/28/14 1/30/14  2/5/14 2/9/14  2/13/14	Mitral stenosis, auricular fibrillation		50 53  49 48  55	

—CALORIMETER RESULTS COMPARED

Arterio sclerosis (radial)	Resp Rate	Dyspnea	Ortho pnea	Periodic Resp	Cyanosis	Edema	Alveolar CO <sub>2</sub> Tension, mm	R Q	Metab % Devia tion from Av Norm	
0	36	+	+	+	Slight	0	2/12=39 2/16=40 2/27=41.6	0.739	+18	
0	26-28	Slight		0	Slight		2/13=44.2	0.791	+19	
0	27-25	—	+	0	Slight	+	2/15=27.8 2/16=33.7	0.753	+28	
0	22-18	0	0	0	Slight	0	2/18=35.5 2/23=37.1	0.876	+2	
0	30-24	+	+	0	+	Slight	2/16=38.6	0.733	+15	
0	25-26	Slight		+	0	0	2/19=39.4	0.766	+26	
0	20-18	—	0	0	++	0	2/18=25.2	0.807	—5	
+	23-21	Moderate	+	+	Slight	Slight	2/24=38.9 2/27=40.0	0.789	+49	Died, April 17, 1915
0	30-38	++	+	Slightly	—	Slight	2/25=41.1 2/26=39.9	0.747	+15	
+	25-22	Slight	+	0	—		—	0.837	+23	
+	28-27	+	++	+	Slight	+	—	0.815	+5	
	19-18	Slight	+	0	+		—	0.817	+8	
Slight		Slight				±		0.819	+8	
		Slight				+		0.796	+3	
	24-18	Slight				+		0.827	+1	
		Slight				±		0.815	+1	
++	20-18	Slight			0	0		0.781	+41	
+		0	0		0	0		0.746	+28	
+		0	0					0.744	+20	
		0	0					0.852	±0	Lying flat on back
		0	0					0.814	+4	Steamer chair
0		0	0		+	0		0.822	+9	Flat on back
		0	0		+	0		0.831	+2	Sitting in bed at angle of 30°
		0	0		+	0		0.803	+7	Lying flat on back
		0	0		+	0		0.842	—4	Sitting up at angle of 50°
		0	0		+	0		0.854	+7	Lying flat on back

the seven with slight dyspnea, all showed an increase except the under-developed girl with congenital heart disease. Of the five with no dyspnea, the only one with increased metabolism was the restless and unsatisfactory alcoholic, David K. (Case 14).

Dyspneic patients must do an increased amount of muscular work in their labored breathing, but it is doubtful if this would account for an increase of 10 per cent. Some of the dyspneic patients were rest-

TABLE 3.—PATIENTS WITH MODERATELY SEVERE DYSPNEA, SLIGHT DYSPNEA AND NO DYSPNEA

Subject	Care No.	Pulse	R:Q	Per Cent Increase of Metabolism above the Normal	Arterial CO <sub>2</sub> Tension, mm.
Patients with moderately severe dyspnea					
Arthur V.	1	90	0.75	+4	21.9
Fred D.	3a	100	0.75	+8	27.8
Edward M.	4	78	0.717	+15	28.6
Henry R.	8	110	0.747	+15	29.0
August F.	10	77	0.815	+5	
Patients with slight dyspnea					
Armon W.	2	77	0.71	+10	44.2
Charles L.	5	71	0.70	+20	29.4
Annie T.	6	100	0.807	+5	21.7
Edward W.	7	112	0.78	+40	28.9
Burrell P.	9	66	0.857	+23	
William S.	11	91	0.817	+8	
Marcus R.	13	81	0.781	+41	
Patients with no dyspnea					
Fred D.*	3b	105	0.753	+2	37.1
George M.	12	70-61	0.50-0.83	+1 to +8	
David K.	14		0.74-0.75	+20 to +28	
William A.	15	61	0.81-0.85	0 to +4	
Theodore S.	16	48-55	0.80-0.85	-7 to +4	

\* Compensated

less while in the calorimeter, but a similar degree of restlessness in other patients does not increase the metabolism more than about 10 per cent. This factor may be of some importance in the cases of Arthur V. (Case 1), Edward M. (Case 4), Edward W. (Case 7), Burrell P. (Case 9) and David K. (Case 14), but other patients with high metabolism for example, Armon W. (Case 2), Fred D. (Case 3), Charles L. (Case 5), Henry R. (Case 8) and Marcus R. (Case 13) were as quiet as the normal controls. It is evident that most dyspneic

patients show a metabolism increased from some cause other than muscular activity

An analysis of the relation between increase of metabolism in these cases and acidosis is of considerable interest. It is unfortunate that the carbon dioxide tension of the alveolar air was not determined in all the patients. The lowest carbon dioxide was found in Case 6 (Annie T.), but it is quite possible that in such a case of congenital heart disease the decreased alveolar carbon dioxide might not be accurate evidence of the change in the reaction of the blood. Excluding this patient, the two with the lowest carbon dioxide, Arthur V. (Case 1) and Fred D. (Case 3) showed marked increase in metabolism. Still there were two others with high metabolism (Edward W., Case 7, and Charles L., Case 5) whose alveolar carbon dioxide was very slightly depressed.

It is interesting to note that patients with low excretion of phenolsulphonephthalein, Arthur V. (Case 1), Charles L. (Case 5) and Edward W. (Case 7), showed marked increase in metabolism; but one, August F. (Case 10), whose phenolsulphonephthalein was low, showed no increase.

Six patients gave systolic blood pressure readings of 170 mm. or over. Of these four, Charles L. (Case 5), Edward W. (Case 7), Marcus R. (Case 13) and David K. (Case 14) had high metabolism, while two, August F. (Case 10) and George M. (Case 12), had low metabolism.

It is evident that in so complex a group of subjects as the sixteen cardiacs and nephritics, there are many factors at work. At present it would seem as if no one factor would account for the definite increase in metabolism found in the dyspneic patients. The studies in this subject are being continued.

It is of interest to note that patients with compensated cardiac lesions or with mild nephritis show a metabolism within the normal limits.

#### SUMMARY AND CONCLUSIONS

Sixteen patients with cardiac and cardiorenal disease have been studied, and for the first time the methods of direct and indirect calorimetry have been compared. In this group of cases the two methods have been found to agree within 1.9 per cent.

The respiratory quotient in all cases was within normal limits (0.73 or above). This is opposed to the findings of Kraus and Grafe. The normal quotients and the very close agreement of the direct and indirect calorimetry prove that there is no profound change in the intermediary metabolism.



TABLE 4—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Case 1 (Arthur V.) 2/1/15 75.1 Kg 1.72 Sq M	Prelim	11 19							
	1*	1 22	20.62	20	0.7	40.92	0.771	18.12	91.99
	2†	1 19	20.41	20	0.77	48.47	0.751	85.29	88.82
								182.61	
Case 2 (Armon W.) 2/1/15 69.75 Kg 1.60 Sq M	Prelim	11 1							
	1	1 5	24.11	21.77	0.81	7.78	0.256	72.03	72.01
	2	1 5	23.85	20.77	0.78	28.72	0.256	74.15	71.81
								146.84	
Case 3 (Fred D.) 2/17/15 47.7 Kg 1.294 Sq M	Prelim	11 24							
	1	1 24	27.27	24	0.75	75.91	0.75	77.75	76.63
	2	1 1	24.07	22	0.75	7.41	0.75	76.27	76.63
								159.02	
Fred D. 2/2/15 70.8 Kg 1.294 Sq M	Prelim	11 19							
	1	12 10	19.07	14.77	0.81	24.00	0.231	50.76	56.63
	2	1 10	20.65	16.9	0.88	25.27	0.251	57.38	60.43
	3	1 10	18.82	18.87	0.81	12.08	0.251	29.96	29.00
								117.70	
Case 4 (Idw M.) 2/17/15 68.88 Kg	Prelim	11 29							
	1	12 9	27.25	27.41	0.76	29.72	0.229	76.57	89.58
	2	1 9	26.87	26.27	0.74	27.51	0.229	85.49	90.02
								162.86	
Case 5 (Chas L.) 2/19/15 85.64 Kg	Prelim	11 23							
	1	12 25	28.50	27.18	0.76	35.43	0.287	89.66	89.41
	2	1 23	20.50	28.84	0.77	29.05	0.287	97.71	93.28
								183.67	
Case 6 (Annie L.) 2/20/15 26.27 Kg 1.016 Sq M	Prelim	10 57							
	1	11 57	16.29	15.60	0.81	20.09	0.150	45.83	43.83
	2	12 57	15.20	17.78	0.80	20.78	0.150	46.02	43.80
								91.85	
Case 7 (Idw W.) 2/24/15 54.35 Kg	Prelim	11 18							
	1	12 18	28.00	26.69	0.79	47.27	0.357	88.64	89.35
	2	1 18	20.78	28.29	0.79	47.66	0.357	94.21	94.88
								182.85	
Case 8 (Henry R.) 2/26/15 75.49 Kg 1.73(?) Sq M	Prelim	11 32							
	1	12 32	24.62	24.07	0.74	38.36	0.303	79.21	77.30
	2	1 32	24.75	23.98	0.75	40.81	0.303	78.91	80.88
								158.12	

\* 63 min

† 57 min

‡ 30 min

## —CALORIMETER EXPERIMENTS

[illegible]

TABLE 4—CALORIMETRY—

Subject Date Weight Surface Area, $\text{sq. m.}$ Formula	Period	End of Period	Carbon Dioxide, G.	Oxygen, Gm.	R. Q.	Water, Gm.	Urine & per Hour, Gm.	Indirect Calo- rimetry, Cal.	Heat Elimi- nated, Cal.
Case 9 (B. and P.) 4/1 70.8 Kg 1.77 sq. M.	Prelim	11 10							
	1	1 10	9.24	27.0	0.8	27.5	0.544	94.29	88.64
	2	1 10	27.8	87	0.85	26.84	0.44	<u>79.57</u> 173.86	50.20
Case 10 (Aug. P.) 7/1/14 59.1 Kg 1.47 sq. M.	Prelim	12 00							
	1	1 00	18.5	15.4	0.8	—	—	Approx 22.50	4.62
	2	2 00	18.75	17.5	0.77	—	—	<u>57.27</u> 100.77	51.67
Case 11 (Wm. S.) 4/10/14 60 Kg 1.62 sq. M.	Prelim	11 30							
	1	1 30	22.65	19.0	0.84	22.45	0.217	65.97	65.20
	2	1 30	21.75	18	0.83	21.97	0.515	<u>72.49</u> 138.47	71.41
Case 12 (Geo. M.) 4/7/15 54.2 Kg	Prelim	10 00							
	1	12 00	40.00	74.5	0.8	40.1	0.202	117.92	104.15
	2	2 00	28.75	60.4	0.79	40.74	0.702	<u>118.02</u> 235.94	115.02
George M 4/14/14 57.15 Kg	Prelim	10 00							
	1	12 00	26.3	72.53	0.82	45.23	0.211	107.57	101.33
	2	2 00	20.8	57.54	0.78	40.45	0.311	<u>123.65</u> 231.53	112.01
George M 3/21/14 58.82 Kg	Prelim	11 30							
	1	12 30	19.21	16.27	0.85	27.14	0.385	54.85	61.39
	2	1 30	20.63	18.41	0.79	25.03	0.785	<u>61.10</u> 115.95	65.63
George M 4/4/14 58.03 Kg	Prelim	11 40							
	1	12 30	22.70	21.12	0.73	26.32	0.402	60.74	63.57
	2	1 40	16.14	13.84	0.55	18.94	0.402	<u>46.44</u> 116.18	46.33
Case 13 (Marcus R.) 4/9/19 63.43 Kg	Prelim	10 00							
	1	12 00	55.21	52.33	0.77	63.56	0.456	172.64	148.96
	2	2 00	55.27	50.59	0.80	74.22	0.456	<u>168.03</u> 340.67	162.03
Case 14 (David K.) 3/21/13 62.66 Kg	Prelim	9 40							
	1	10 40	25.86	25.57	0.74	32.26	0.323	83.84	79.94
	2	11 40	21.78	20.91	0.76	28.71	0.323	<u>68.89</u> 152.73	66.49
	3	12 40	27.13	26.95	0.73	32.44	0.323	83.36	82.37
	4	1 40	29.85	27.43	0.78	32.74	0.323	91.04	84.83
	5	2 40	25.50	23.78	0.78	30.95	0.323	78.89	80.54
	6	3 40	23.74	23.61	0.73	30.16	0.323	<u>77.32</u> 488.34	79.79

—EXPERIMENTS—(Continued)

[illegible]

TABLE 4—CALORIMETRY—

Subject, Date, Weight, Surface Area, Linear Formula†	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine & per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
David K 12/11/14 68.1 Kg	Prelim	10 1	.	.	.	.	.	.	.
	1	10 21	22.51	21.75	0.72	27.1	0.24	74.57	68.55
	2	11 11	22.60	21.75	0.76	27.75	0.291	71.65	67.05
								146.61	
Case 10 (Wm A) 12/15/14 65.44 Kg 17.5 Sq M	Prelim	11 12	.	.	.	.	.	.	.
	1	12 13	21.52	20.51	0.84	24.5	0.222	62.44	72.58
	2	1 13	21.65	20.54	0.84	25.15	0.222	70.14	72.08
	3	2 13	21.45	20.6	0.83	24.11	0.222	73.44	73.48
								215.02	
William A 1/27/15 65.60 Kg 17.4 Sq M	Prelim	10 40	.	.	.	.	.	.	.
	1	11 40	21.57	21.65	0.84	25.70	0.220	70.56	73.83
	2	12 40	22.01	21.17	0.82	24.57	0.220	74.01	75.83
	3	1 40	21.75	22.0	0.78	22.53	0.220	76.55	78.06
								221.83	
Case 10 (Theo S) 1/28/14 69.52 Kg 16.8 Sq M	Prelim	11 10	.	.	.	.	.	.	.
	1	12 10	21.15	20.20	0.83	24.03	0.454	67.86	77.28
	2	1 10	22.05	21.45	0.81	25.25	0.454	71.40	76.66
								139.26	
Theodore S 1/30/14 69.44 Kg 16.5 Sq M	Prelim	11 15	.	.	.	.	.	.	.
	1	12 15	21.66	18.76	0.84	20.00	0.385	62.97	73.11
	2	1 15	22.50	20.18	0.82	37.75	0.385	67.45	73.83
								130.45	
Theodore S 2/5/14 66.28 Kg 16.9 Sq M	Prelim	11 46	.	.	.	.	.	.	.
	1*	1 10	24.63	21.50	0.80	50.61	0.538	105.10	118.65
	2	2 10	22.82	20.73	0.81	32.00	0.539	68.47	72.40
								173.57	
Theodore S 2/9/14 61.15 Kg 17.0 Sq M	Prelim	11 50	.	.	.	.	.	.	.
	1	12 50	21.11	18.41	0.83	21.14	0.394	61.66	56.93
	2	1 50	22.34	19.11	0.85	22.55	0.394	64.30	60.88
								135.96	
Theodore S 2/13/14 61.99 Kg 17.1 Sq M	Prelim	11 10	.	.	.	.	.	.	.
	1	12 10	24.54	20.49	0.87	26.78	0.391	69.38	70.40
	2	1 10	24.35	21.15	0.84	33.09	0.391	71.02	75.79
								140.40	

\* 1½ hours

† In the case of Theodore S the height weight formula

—EXPERIMENTS—(Continued)

[illegible]

Case 15, William A Jan 7 8, 1915	2,753	941	1260	2915	1505	1389	157	-0.2		1.5	12.5
Jan 8 9, 1915	3,075	1122	1329	2914	1755	1882	152	-2.5		1.50	
Jan 9 10, 1915	3,207	974	1319	255	1725	1474	166	-0.48		1.50	
Jan 25 26, 1915	1,736	720	900	1316	1112	972	1067	-0.55		1.52	1744
Jan 26 27, 1915	2,538	764	1028	2917	1215						
Jan 27 28, 1915	2,043	583	871	1674	922	1020	1173	-1.01		1.15	6260
Case 5, Charles L Feb 19 20, 1915	1714	733	798	1774	535	255	968	-2.75		1.5	5581
Case 8, Henry R. Feb 26 27, 1915	1,055	182	531	1525	291	712	741	-1.0		1.17	7470
Case 3, Fred D Feb 15-16, 1915	830	316	797	799	566	1541	1512	-8.06		1.5	6570
Feb 16 17, 1915	711	215	580	576	22	148	1107	-10.75		1.50	
Feb 17 18, 1915	832	333	792	726	566	1109	116	-6.1	6.5	1.50	
Feb 18 19, 1915	1,155	311	485	1574	550	769	846	-2.55	6.6	1.80	
Bartolo D Mar 11 12, 1915	2,870	579	1677	1699	1374	668	755	16.0		1.50	
Mar 12 13, 1915	2,922	1095	1715	3117	3413	572	119	9.17		1.54	478
Mar 13 14, 1915	3,498	669	1921	2906	1570	717	572	10.78		1.59	6785
Mar 14 15, 1915	2,083	918	1876	2722	1109	1259	876	16.77		1.70	478
Mar 15 16, 1915	2,317	787	1190	2164	1573	669	771	4.7		1.5	4149
Morris S Dec 17 18, 1914	1,920	766	750	3412	965	1169	169	-3.4		1.75	4191
Dec 11 18, 1914	538 Protein metd	621	118	171	969	624 Cal 816cc				6.40 816cc	
Case 9, Burrell P Mar 24 25, 1915	2,206	711	1210	2100	1113	1227	1571	-2.13		1.65	7081
Case 11, William S Feb 10 11, 1915	1,726	400	953	1619	649	1061	1125	-1.69		2.25	1562
Feb 11 12, 1915	2,444	599	1174	2697	960					1.69	
Case 7, Edwin W Feb 24 25, 1915	1,423	112	539	1696	767	756	798	-0.91		1.254	5459
Case 16, Theodore S Jan 28, 1914	2,021	884	948	1695	141					8.04	7955
Jan 29, 1914	2,034	963	873	2017	154					1.027	6010
Jan 30, 1914	2,055	954	911	1915	153					9.0	5948

† Urine N + 10% of food N

Patients with compensated cardiac lesions or with mild nephritis showed no increase in the metabolism. Of twelve patients with dyspnea, nine showed a distinct rise in metabolism, and in five of these the increase was from 25 to 50 per cent above the average normal. Two out of the five gave evidence of marked acidosis in the low content of carbon dioxide in the alveolar air. In two others, whose metabolism was just as high, there was no significant depression of the alveolar carbon dioxide.

697 Huntington Avenue, Boston—477 First Avenue, New York

#### REPORT OF CASES

CASE 1—Arthur V., aged 40, Italian, admitted Feb 10 1915, discharged March 3, 1915. Service of Dr. Nammack.

Diagnosis. Chronic nephritis, chronic myocarditis with decompensation.

Complaint. Dyspnea and cough.

Past History. Never sick before except for an attack of bronchitis three months ago. No history of venereal disease.

Present Illness. Has been "feeling poorly" for one month. For twelve days has had shortness of breath.

Physical Examination (February 12). The patient is a well built and fairly well developed man. Height 155 cm. Skin is slightly yellowish. Sclerae clear. He is dyspneic and orthopneic. There is a slight cyanotic tinge to his lips and ears. Respiration is rapid and shallow, rate 30. Pneumographic tracings show respiration to be periodic in type. Heart. Dulness extends from 16 cm to the left of the midsternum in the fifth space to 5 cm to the right in the third space. The action is regular. At the apex there is a weak first sound with a faint systolic murmur and a weak second sound. Gallop rhythm at the apex. Pulmonic second sound is louder than the aortic second sound. No murmurs at the base. Radial artery not palpable. Lungs. Slight dulness at extreme right base posteriorly. Large moist rales at both bases. Abdomen, negative. Liver. Dulness extends 3 cm below the costal margin. Edge indistinctly felt. No edema.

Pulse. Varied in rate from 72 to 116 between February 10 and February 18.

Temperature. Between February 10 and February 18 varied between 97.8 and 101 F except on February 13, when it reached 103 F (rectal), February 16, when it was 102.2 F (rectal), and February 17, when it was 102.4 F (rectal).

Urine. February 10, specific gravity, 1.026, albumin, very faint trace. One hyaline cast.

February 14, specific gravity, 1.020, albumin, cloud. Few casts.

February 23, specific gravity, 1.020, albumin, faint trace. No casts.

Blood Pressure. February 15, systolic, 110 mm, diastolic, 70 mm.

February 16, systolic, 120 mm, diastolic, 75 mm.

February 24, systolic, 120 mm, diastolic, 60 mm.

Phenolsulphonephthalein Test. February 15, first hour, 20 per cent, second hour, 12 per cent, total, 32 per cent.

February 27, first hour, 50 per cent, second hour, 13 per cent, total, 63 per cent.

March 2, 1915. Roentgenoscopy does not reveal evidence of aneurysm or dilatation of the aorta. Cardiac shadow is triangular in shape with enlargement of the right heart. Cardiophrenic angle is obtuse.

Medication. Patient was on a "soft special" diet, consisting chiefly of milk, cream, bread, butter and eggs. Strophanthin, 0.5 mg, intramuscularly, on February 10. Digitalis from February 13 to February 22, inclusive.



## DIET CHART SUMMARY

Date	Food Calories	Food N, Gm.	Urine Vol Cc	Urine N, Gm
2/12/13	1246	728	540	1027

Alveolar Air (Plesch-Higgin's method) February 12, 239 mm, February 16, 308 mm, February 27, 410 mm

Electrocardiogram February 26 "R" wave small in all leads, directed down in lead 3 "P" waves larger in all leads

In the ten days following the observations in the calorimeter, the patient's condition showed little change. His dyspnea, though of only moderate grade while he was at rest, improved but little. Physical examination remained practically unchanged.

In calorimeter, Feb. 12, 1915, No. 189

February 13, the dyspnea is somewhat less marked. The pulse is a little smaller and the heart action not quite so strong.

February 26, seems improved. Much less dyspnea. Pulse suggestive of a Corrigan.

CASE 2—Armon W., aged 33, pedler, born in Hungary, admitted Feb. 9, 1915, discharged Feb. 18, 1915. Service of Dr. Nammack.

Diagnosis: Mitral stenosis and insufficiency. Auricular fibrillation.

Complaint: Pain in heart and right side.

Past History: Was never sick up to six months ago. Has been in hospitals twice during last six months on account of dyspnea and swollen feet. No history of rheumatism or syphilis.

Present Illness: No improvement since discharged from Beth Israel Hospital.

Physical Examination (February 13): Patient is a fairly well built young man. Height 161 cm. Respiration, 28 per minute. Slight cyanosis. Heart dulness extends from 12 cm. to left of the midsternum in the fifth interspace to the right sternal border of the sternum. First sound at apex is loud and is followed by a rumbling systolic murmur. Second sound is loud and is followed by a rumbling diastolic murmur which extends through the short diastoles but is followed by a pause before the first sound in the longer diastoles. Both second sounds are normal at the base. Action absolutely irregular. Practically all the beats reach the wrist.

Temperature: Normal.

Pulse: From 156 to 72.

Respiration: From 26 to 28. During last three days it was from 20 to 24.

Medication: Special diet. Infusion of digitalis, every four hours from February 9 to 10.

Wassermann (Feb. 10, 1915) + + +

Blood Pressure (February 18) Systolic, 110, diastolic, 70.

Urine February 10 specific gravity, 1.022, albumin, 0, no casts.

February 17, specific gravity, 1.030, albumin, faint cloud, no casts.

Alveolar Air (Plesch method) February 13, carbon dioxide tension 44.2 mm. In calorimeter Feb. 13, 1915.

CASE 3—Fred D., aged 17, clerk, admitted Feb. 13, 1915, discharged March 19, 1915. Service of Dr. Nammack.

Diagnosis: Mitral stenosis and insufficiency.

Complaint: "Shortness of breath."

Past History: First attack of rheumatism at the age of 6 years. He made a complete recovery and was well until a second attack of rheumatism at 11 years of age. Since then he has been perfectly well up to the present illness.

Present Illness: Began three weeks ago with pain in the abdomen. He stopped work for one week but after that went back to work for two weeks. During the week before admission to the hospital he was troubled with marked shortness of breath. Edema of feet began on the day before admission. He has had a cough for three days.

Physical Examination (February 16). The patient is 157 cm tall. He is slightly cyanotic and orthopneic. No clubbing of fingers. Heart Apex impulse is in the fifth space 9 cm to the left of the midsternal line. Cardiac dullness extends from 12 cm to left of midsternum in the sixth space to 5 cm to the right in the fourth space. Action regular. At the apex the first sound is followed by a blowing systolic murmur, the second sound is distant and followed by a long rumbling murmur which extends through diastole. The pulmonic second sound is accentuated. There is a loud systolic murmur in the fourth and fifth spaces just to the left of the sternum and transmitted to the right. The lungs are negative except for scattered rales and dullness at the extreme left base. Liver not felt. Abdomen negative. Slight edema of legs.

Urine Specific gravity, 1.030, heavy cloud of albumin, many casts.

Temperature has ranged from 100 to 102 since admission.

Pulse has varied between 96 and 112, respirations from 24 to 32.

The patient was in the calorimeter, February 15, the day preceding the foregoing physical examination, and on February 23.

February 19. The patient is now almost completely compensated at rest. Respiration less rapid and less labored. Slight cyanosis persists. Heart dullness extends from 10 cm to the left in the fifth space to 3.5 cm to the right in the fourth space. Action regular. Sounds and murmurs are unchanged. He has been passing large quantities of water.

Date	Food Cal	Food N	Urine N	Urine NaCl	Urine Vol, Cc
2/15-16			12.61		913
2/16-17	518	3.92	14.28		2,430
2/17-18			11.69	26.95	4,800
2/18-19	1,139	4.90	7.90	20.48	1,880

February 24. Blood pressure systolic, 95, diastolic, 70.

February 17-24, temperature varied between 98.4 and 99.8 (rectal).

February 20. Urine Albumin negative, no casts.

The patient was on the Karrell diet and received digitalis from February 14 to February 17, inclusive.

February 24. Blood culture sterile. Wassermann negative.

March 13. Up and about.

Alveolar Carbon Dioxide (Plesch-Higgins method). February 15, average 27.7 mm, February 16, average 33.7 mm, February 18, average 36.7 mm, February 23, average 37.2 mm.

Medication. Digitalin, 10 minims every four hours (8, 12, 4) the night before going into the calorimeter (Feb 15, 1915). Also digitalin, 10 minims, every four hours (8, 2, 6) on the day of the calorimeter (Feb 15, 1915).

No electrocardiogram.

CASE 4—Edward M., aged 37, chauffeur, born in the United States, admitted Feb 15, 1915, discharged Feb 27, 1915. Service of Dr. Coleman.

Diagnosis. Mitral insufficiency and auricular fibrillation.

Complaint. Dyspnea and edema of the legs.

Family History. Negative.

Past History. Had rheumatism in 1908. The attack lasted about one year, and affected all the joints of his limbs. He was in bed off and on. Four years ago he was refused life insurance. He has had dyspnea, palpitation, edema of the feet and vertigo for several years. During the last year these symptoms have been severe. This is his third admission to the hospital since last May. No history of venereal disease.

Present Illness. Legs have been more swollen during the last week. Dyspnea and cough are more severe, so he has returned to the hospital.

Physical Examination (Feb 17, 1915). The patient is a large, well developed man. He is orthopneic and distinctly cyanotic, but his respiration is

slower and not so labored as it was yesterday. He coughs occasionally but raises little sputum. Heart Dulness extends from 14 cm to the left of the midsternum in the fifth space to 4 cm to the right in the fourth space. Pulse 86, irregular in force and rhythm. No pulse deficit. At the apex the first sound is poor in quality, and is followed by a blowing systolic murmur which is transmitted to the left. No murmurs at the base. Pulmonic second sound at the left base posteriorly. Radial artery not palpable. Lungs. Slight dulness at the chest. Liver. 1 dec indistinctly made out 5 cm below the costal margin in the right mammary line. No fluid in the abdomen. Slight edema of the feet and legs.

Pulse, between February 16 and February 20, ranged from 56 to 108. It was 120 once and 140 once.

Temperature reached 102.1° (rectal), February 16. From then to February 20 it was below 99.8° F. (rectal).

Respiration varied from 24 to 30 on the first three days in the hospital, and was subsequently 20 or less.

Blood Pressure. February 16, systolic, 120, diastolic 85.

Urine. February 16, specific gravity, 1.025, trace of albumin, no casts.

Medication. Soft diet. Digitalis from February 16 to February 19, infusion of digitalis, 20 minims, the night before and on the day he was in the calorimeter.

Alveolar Air (Plesch method). February 16, carbon dioxide tension, 38.3 mm.

Electrocardiogram shows auricular fibrillation. 'T' waves directed down in the second and third leads.

Patient regained compensation rapidly, and on February 24 was beginning to get up in a chair.

In calorimeter, Feb. 17, 1915.

Discharged, Feb. 27, 1915. General condition very good. Cyanosis much improved. Walks around without shortness of breath. Pulse still irregular.

CASE 5.—Charles L., aged 54, laborer, born in the United States, admitted February 16, 1915, discharged Feb. 24, 1915. Service of Dr. Lambert.

Diagnosis. Chronic nephritis with hypertension. Cardiac hypertrophy with aortic insufficiency and mitral insufficiency. Emphysema.

Complaint. Shortness of breath.

Family History. Negative.

Past History. Three years ago he was sick for nine weeks with rheumatism. He had erysipelas following a fracture of the skull six years ago. He drinks a considerable amount of beer. There is no history of syphilis.

Present Illness. He has noticed dyspnea for about a month when he went upstairs. For two weeks this has been much worse and he has been unable to sleep at night.

Physical Examination (February 19). The patient is a rather large, strong man. His skin has slight yellowish tinge. Lips and mucous membranes are of fair color. There is no definite cyanosis. Respiration is quiet but somewhat rapid. Respiration is periodic in type, but without intervals of complete apnea. The chest is large, almost barrel-shaped. Heart. Dulness extends from 14 cm in the fifth space to the left of the midsternum to the right sternal margin. No area of absolute cardiac dulness. Action regular. At the apex the first sound is rather faint and it is followed by a blowing systolic murmur. The second sound at the apex is also faint, it is followed by a blowing diastolic murmur. Both systolic and diastolic murmurs are well heard in the axilla and over the precordium. They are also audible in the first and second spaces to the right of the sternum. The murmurs are loudest in the first space to the right and in the second space to the left of the sternum. The pulse is of good size, high tension, and distinctly collapsing in type. Artery wall not palpable. Lungs. Emphysematous. Scattered râles in both sides of back. Fairly frequent cough, but little expectoration. Dulness with absent breath sounds at extreme right base posteriorly. Abdomen negative except for slight tenderness in region of the liver. Liver not felt. No edema.

Temperature Varied between 98 and 100 F (rectal)  
Pulse Varied between 64 and 100  
Respiration Ran between 28 and 36 on the first two days—later between 20 and 28  
Wassermann Reaction Negative  
Blood Pressure February 17, systolic, 180, diastolic, 90  
Phenolsulphonephthalein Test February 20, first hour, 10 per cent, second hour, 20 per cent, total 30 per cent  
Urine February 16, specific gravity, 1 020, albumin heavy cloud, many casts  
February 21, specific gravity, 1 018, albumin strong trace, many casts

#### SUMMARY OF DIET CHART

Date	Food Cal	Food N	Urine Vol, Cc	Urine N	Urine NaCl
2/19-20	1 524	5 82	685	8 55	12 17

Medication Special diet Restricted fluids Infusion of digitalis every four hours from February 18 to February 20 Infusion of digitalis just before going into calorimeter

Alveolar Air (Plesch method) February 19, carbon dioxide tension, 39 4 mm at 3 30 p m

In calorimeter, Feb 19, 1915

CASE 6—Anne T aged 14, born in the United States, admitted Jan 14, 1915, discharged March 25, 1915 Service of Dr Lambert

Diagnosis Congenital heart disease Open ventricular septum Dextrocardia

Complaint Heart trouble, headache and trembling

Family History Negative

Past History Negative except for the dyspnea associated with her cardiac condition

Present Illness Comes to hospital on account of a severe attack of headache, with palpitation of the heart, and stomach ache Has had similar attacks before

Physical Examination Height 137 cm The patient is a small, rather under-developed girl, dull mentally She lies flat on her back breathing quietly but slightly rapidly There is a high degree of cyanosis of lips, tongue, nose, hands and feet There is marked clubbing of the fingers and toes The chest is asymmetrical Right side more prominent than left Heart Apex impulse is in the fifth space 9 cm to the right of the midsternal line The dulness extends from 11 cm to the right in the fifth space to 4 cm to the left of the midsternum in the fourth space No thrills are felt At the apex, just below and outside the right nipple, the first sound is scarcely audible, and there is a loud blowing systolic murmur The second sound is weak There is a loud systolic murmur heard all over the precordium and to the left of the sternum Its maximum intensity is in the fifth space just to the right of the sternum There is a loud, low pitched systolic murmur in the second space just to the left of the sternum, and also in the second space to the right of the sternum Lungs Negative on auscultation and percussion Abdomen, liver and spleen negative Skin harsh and dry

Roentgenoscopy reveals transposition of heart and colon Stomach and liver are in normal position

Temperature Ranges between 98 4 and 101 F (rectal)

Pulse Usually varies between 86 and 108

Respiration Now from 20 to 24

Blood Pressure January 27, systolic, 95 mm

Urine January 15, specific gravity, 1 025, albumin, cloud, granular casts

Alveolar Air (Plesch method) February 18, carbon dioxide tension, 25 2 mm at 4 p m



February 27 The patient has Cheyne-Stokes respiration—periods of apnea and periods of intense dyspnea He is very uncomfortable with his breathlessness His condition appears to be much worse

In calorimeter, Feb 24, 1915

March 7, 1915 Patient has improved very little Fairly comfortable during the day, but each night suffers from shortness of breath and great restlessness Heart action is rapid, and there is a gallop rhythm in spite of digitalis Respiration is of Cheyne-Stokes type Left hospital against advice in a serious condition Died April 17, 1915

CASE 8—Henry R, aged 40, born in the United States, waiter, admitted to hospital, Jan 22, 1915, died March 20, 1915 Necropsy not obtained Service of Dr Nammack

Diagnosis Chronic myocarditis Emphysema Chronic nephritis (?)

Complaint Shortness of breath

Past History Syphilis three years ago Was in Bellevue Hospital in May, 1914, with lobar pneumonia Has been in hospital since then with diagnosis of chronic myocarditis the first time, and chronic cardiac valvular disease the second time Drinks two or three whiskies a day

Present Illness Comes into the hospital again because of increase of dyspnea since catching cold On admission the clinical picture was that of an acutely decompensated heart February 6, he began to run an irregular temperature, reaching sometimes 103, rectal The diagnosis of bronchopneumonia was considered February 21, the temperature fell to normal Since then the highest temperature has been 101, rectal General condition has not improved essentially

Physical Examination (February 26) The patient is a big strong negro 153 cm tall Respiration is very rapid and shallow, rate, 40 There is orthopnea Tongue and conjunctiva are rather pale Eyes are prominent Chest is very large Heart Dulness extends from 12.5 cm to the left of the midsternum in the fifth space to 3 cm to the right in the fourth space The action is regular and rapid Sounds are of fair quality No murmurs are heard There is a well marked protodiastolic gallop rhythm, heard best just below and outside the left nipple Aortic second sound is slightly accentuated and ringing Pulse is of fair quality, rate, 116 per minute Artery wall not palpable Lungs Marked emphysema Slight dulness at extreme right base posteriorly A few scattered râles throughout both lungs Many moist râles at the right base behind Abdomen, negative Liver Edge easily felt about 3 cm below the costal margin in the right nipple line Slight tenderness over the liver Very slight edema of the feet and lower legs

Urine Clear, amber, 1.022 specific gravity, acid, heavy cloud of albumin, many hyaline and coarsely granular casts, many leukocytes

Blood Pressure February 18, systolic, 138, diastolic, 105

February 27, systolic, 160, diastolic, 120

Phenolsulphonephthalein Feb 27, 1915, first hour, 30 per cent, second hour, 18 per cent, total, 48 per cent

Wassermann, January 30, double positive, 12 units

Alveolar Air (Plesch-Higgins method) February 25, carbon dioxide tension, 41.1 mm at 5 p m February 26, carbon dioxide tension, 39.9 mm at 4.30 p m

Medication Soft diet Morphine Infusion of digitalis Tincture digitalis Codein  $\frac{1}{4}$  grain, the night before and the morning before going into calorimeter

Temperature January 22 to Jan 28, 1915, 99 to 101 January 28 to Feb 1, 1915, 99 February 2 to Feb 7, 1915, rose to 103.5 once February 8 to Feb 12, 1915, 100 to 101.5 February 12 to Feb 16, 1915, 100 to 104 Remainder of time, 99 to 101

In calorimeter, Feb 26, 1915

CASE 9—Burrell P, aged 41, laborer, admitted March 18, 1915, discharged April 5, 1915 Service of Dr Nammack

Diagnoses Aortic regurgitation and stenosis Mitral regurgitation Tricuspid regurgitation Aneurysmal dilatation of the aorta

Chief Complaint Shortness of breath

Past History Measles and whooping cough as child Pneumonia twenty years ago

Present Illness Duration for past year Ten weeks ago found that he could not work properly on account of shortness of breath Has had hoarseness and sore throat Nocturia rather frequent Occasional headaches Marked dyspnea, especially after work Has had no swelling of ankles or legs at any time Coughs frequently and has marked night sweats

Physical Examination (March 23, 1915) Patient is a dark negro of muscular development Is 169 cm (5 feet 7 inches) tall Orthopneic and dyspneic, breathing 26 to the minute Not prostrated nor in much distress An occasional unproductive cough Heart Apex beat in sixth space, 15 cm to the left Action is regular, not rapid, forceful At the apex there is a blowing systolic murmur transmitted to the left, and a waterfall diminuendo diastolic murmur heard with maximum intensity to the left of the sternum, but audible over the whole precordium In the third left space there is a short presystolic murmur (Flint?) Over the aortic region there is a harsh systolic and a soft diastolic murmur Pulse Large excursion, quick rise and fall Artery wall moderately thickened Lungs No dullness, many sibilant and sonorous râles Cervical, axillary, epitrochlear, inguinal glands considerably enlarged

March 19 1915 Electrocardiogram shows a large "P" wave and the "T" wave is directed upward in each lead There is marked left sided preponderance

April 1, 1915 Some dyspnea Complaints of precordial pain Heart not much changed

Urine Negative

Blood No data

Temperature ran to 101.5 F, March 18, 1915, below 100 F the rest of the time

Pulse March 18 1915, from 104 to 112, March 19, 1915, from 70 to 80

Respiration March 18, 1915, from 20 to 32

In the calorimeter, March 24, 1915

March 18, 1915 Pupils unequal React sluggishly Aortic arch is dilated and heart is greatly enlarged down and to the left, also to the right of the midsternal line Systolic thrill palpable over the aortic area Apical impulse is forceful Systolic and diastolic murmur is heard at the apex Aortic second sound is accentuated A systolic murmur is heard over the tricuspid area There is an extracardiac sound heard which appears to be a pericardial rub The pulse is of a typical Corrigan type

March 22, 1915 Condition improved Rhythm regular Rate slow Pericardial scratch persists Seems much better compensated

Medication Digitalin, 15 minims, every four hours, the day before going into the calorimeter Also  $\frac{1}{4}$  grain codein, the night before going into the calorimeter

CASE 10—August F, aged 62, tailor, married, admitted April 26, 1915, died May 20, 1915

Diagnosis Chronic interstitial nephritis and auricular fibrillation

Complaint Shortness of breath Swelling of feet Pain in chest

Past History There is a family history of cardiac disease He was told that he had albumin in the urine many years ago He had pneumonia long ago Has had no rheumatism Three months ago fluid was removed from his chest

Present Illness Began three years ago with a feeling of fatigue and shortness of breath He has had remissions ever since Also occasional headaches and night sweats He feels very weak

Physical Examination The patient is 159 cm tall He is very orthopneic and in considerable distress His lips are dry and cyanotic Teeth are bad

There are many râles over both bases of the lungs Heart Right border 3 cm from the midsternal line Upper border at the third rib Left border 14 cm and the apex 13 cm from the midsternal line There is a faint systolic blow heard over the apex The sounds are of poor muscular quality There is a harsh systolic murmur heard over the aortic area The pulse is somewhat irregular Walls palpable

April 27 Pulse slower after strophanthin and digitalis

April 29 A rough, hard systolic murmur is heard over the base of the heart, loudest in the third left space The second sound is also loudest in this site There is a moderate amount of fluid in the abdomen Edema of the extremities

May 1 Dulness at both bases posteriorly Breath sounds diminished in intensity at the bases, where one hears an occasional râle The cardiac impulse is less pronounced than on admission The heart is still much dilated There is a rough blow at the mitral area The aortic second sound is slightly prolonged The heart impulse is in the fifth space 12 cm to the left of the midline The left limit of dulness is in the sixth space, 12.5 cm to the left of the midline Right limit of dulness is in the fourth space, 4 cm to the right of the midline There is a systolic murmur of maximum intensity to the right of the sternum The patient has very scant beard Pubic hair of female type The patient is very orthopneic distinctly dyspneic and shows marked Cheyne-Stokes breathing when asleep or quiet He is slightly cyanotic There is distinct edema of the flanks and legs The breath is slightly urinous

Urine Cloudy, amber colored, specific gravity, 1.010, trace of albumin, hyaline and granular casts, leukocytes, erythrocytes

Blood Pressure Systolic, 170, diastolic, 110 (?), May 1, 1915

Blood Leukocytes, 15,600, polymorphonuclears, 68 per cent, transitionals, 3 per cent, lymphocytes, 25 per cent, large mononuclears, 4 per cent

Temperature April 27 to May 12, from normal to 100, May 13 to May 19, 103

Respiration During high temperature, from 24 to 32

Pulse During high temperature, from 104 to 120

Electrocardiogram May 3, shows auricular fibrillation and left hypertrophy

Phenolsulphonephthalein Test May 8, first hour, 13 per cent, second hour, 11 per cent, total, 24 per cent

The patient grew more and more orthopneic and dyspneic until death Breath became more urinous

CASE 11—William S, aged 48, longshoreman, admitted Dec 22, 1914, discharged March 1, 1915 Service of Dr Coleman

Diagnosis Adherent pericardium and auricular fibrillation

Complaint Shortness of breath Pain in lumbar region

Past History Healthy until 1913, when he had pneumonia and was in Ward B2 of the Bellevue Hospital After discharge he was weak and dyspneic for two months and was unable to work Since then he has had a productive cough He has lost weight and has had hemoptysis There is a positive history of syphilis and gonorrhea

Present Illness Dec 22, 1914, while unloading heavy lumber, he became suddenly short of breath He rested but obtained no relief

Physical Examination The patient is 171 cm tall, a moderately well nourished man, propped up in bed, markedly dyspneic and somewhat cyanotic Pupils are sluggish He is breathing rapidly and shallowly There is diffuse systolic impulse over a broad area at the apex The area of absolute cardiac dulness is very much enlarged The sounds are of poor quality There are no murmurs The abdomen is distended and somewhat tender The liver is felt at the umbilicus Heart Right border is 10 cm to the right of the midline, left border, 14 cm to the left of the midline A triangular area of dulness

Wassermann Anticomplementary



Jan 2, 1915 General condition much improved Broadbent's sign present  
 Jan 27, 1915 Patient sat up for two hours without any ill effect  
 Feb 3, 1915 Three days ago the patient developed shortness of breath, precordial pain, edema of the extremities

Feb 10, 1915 Dyspnea less marked Cyanosis persists Heart action very irregular, sounds faint, no distinct murmurs Regurgitant wave in the jugulars Few moist râles at bases

Feb 28, 1915 Distention of abdomen relieved by catharsis Dyspnea continues Heart irregular Condition improved slightly

Urine Dec 23, 1914, clear, pale amber, specific gravity 1020, acid, faint trace of albumin, few hyaline casts

Blood Dec 24, 1914, leukocytes, 4,800, polymorphonuclears, 73 per cent, transitionals, 5 per cent, lymphocytes, 12 per cent, large mononuclears, 8 per cent, eosinophils, 1 per cent

Temperature December 23 to December 25, from 101 to 103 F December 26 to Feb 28, 1915, from normal to 99 F

Pulse In the beginning from 100 to 146, later, from 60 to 80, then from 80 to 95

Respiration In the beginning, from 28 to 36, later, from 24 to 28

Blood Pressure Dec 26, 1914, systolic, 110, diastolic, 80 (?)

Electrocardiogram December 28, auricular fibrillation, "T" waves directed down in all leads

Röntgenoscopy December 30, moderate enlargement to the right and left, marked irregularity in the outline of the right diaphragm suggesting extensive adhesions

In calorimeter, Feb 10, 1915

CASE 12—George M., aged 56, saloonkeeper, watchman, porter, admitted Jan 19, 1914, discharged April 29, 1914 Service of Dr Meara

Diagnosis Chronic interstitial nephritis and cardiac hypertrophy

Complaint Shortness of breath Swelling of the feet

Past History Alcoholic Had measles when a child Gonorrhea thirty-four years ago

Present Illness In December, 1911, he first noticed shortness of breath on exertion and swelling of feet after work Had to stop work about the 10th of June, 1911, because of the shortness of breath and edema of feet His abdomen then began to increase in size and he became yellowish in color His scrotum and penis began to swell Frequent micturition Oct 23, 1912, he was taken with shortness of breath again, cough and swelling of the legs Aug 5, 1913, his legs began to swell, and he became very dyspneic on walking His sputum became bloody He could not lie down in bed on account of dyspnea His abdomen increased in size

Physical Examination (Jan 19, 1914) The patient is a well nourished man propped up in bed showing considerable dyspnea His face is flushed and somewhat edematous Chest symmetrical and emphysematous Sibilant and sonorous râles anteriorly and posteriorly Heart Right border 7 cm to the right, left border 13 cm to the left, cardiac impulse 12.5 cm from the midsternal line It extends to the third rib above The sounds at the apex are of poor muscular quality There are extrasystoles, some of which are not felt at the wrist At the base the sounds are distant No murmurs can be definitely made out The pulse is irregular in force and rhythm The vessel walls are slightly thickened Liver dullness extends 2 cm below the costal margin Extremities edematous

Jan 22, 1914 Left lung shows dullness to flatness from the angle of the scapular to the base with a pleuritic rub Heart Left border 13 cm from the midsternal line in the fourth-fifth interspace, right border 7 cm from the midsternal line in the third-fourth interspace Extends to third rib above

Feb 23, 1914 Doing well No edema. Heart regular Patient has a pulsus alternans

March 14, 1914 Looks very well On sodium chlorid has incomplete elimination with formation of an edema and increased blood pressure On potassium chlorid the elimination is complete, associated with diuresis and fall of blood pressure

April 28, 1914 General condition excellent Heart as noticed above Discharged

Urine Nov 10, 1912, cloudy, amber, specific gravity 1.022, acid, faint trace of albumin, finely granular casts, leukocytes +, erythrocytes +

Blood Dec 6, 1912, leukocytes, 11,000, polymorphonuclears, 73 per cent, transitionals, 7 per cent; lymphocytes, 15 per cent, large mononuclears, 8 per cent, hemoglobin, 90 per cent, reds, 4,504,000

Blood Pressure March 24, 1914, systolic, 195, diastolic, 115 April 4, 1914, systolic, 160, diastolic, 102

Pulse March 24, 1914, from 72 to 90, April 4, 1914, from 72 to 80

Respiration March 24, 1914, from 18 to 24, April 4, 1914, from 20 to 24

Temperature. March 24, 1914, subnormal, April 4, 1914, subnormal

Wassermann Dec 8, 1913, positive

Phenolsulphonephthalein Jan 27, 1914, 55 per cent in two hours

CASE 13—Marcus R, aged 51, Hebrew, tinsmith, admitted March 10, 1913, discharged April 12, 1913 Service of Dr Thompson

Diagnosis Chronic interstitial nephritis, arteriosclerosis, mitral insufficiency

Past History He had malaria at the age of 17 to 20 years Had pneumonia in 1877 He is a moderate user of alcohol, occasionally took whisky before breakfast

Present Illness In January, 1912, his legs began to swell Since then he has been short of breath and has not been able to walk He has been very thirsty and gets up once or twice at night to pass water Three weeks ago he caught cold

Physical Examination The patient is of medium stature and heavy build He is slightly dyspneic The apex is in the fifth space, 14 cm from the midline The sounds are booming There is a loud systolic murmur at the apex The aortic second sound is very much accentuated The artery wall is very thick, and there is a question of calcification Tension is high Pulse is regular Many crackling and moist râles over the lungs Liver edge is felt one hand's breadth below the costal margin The surface is hard and nodular There is shifting fluid in the flanks

Urine March 10, from 600 to 1,400 c c

Blood Pressure March 10, systolic, from 300 to 320, diastolic, from 140 to 180 March 16-31, systolic, 300 to 310, diastolic, 115 to 150 April 1-9, systolic, 300 to 320, diastolic, 150 to 170

Temperature March 10, from 98 to 100 F March 16-31, normal April 1-9, normal

Pulse March 10, from 88 to 100 March 16-31, 72 to 80 April 1-9, 78 to 84

Respiration March 10, from 20 to 30 March 16-31, 18 to 20 April 1-9, 18 to 20

Weight March 10, 149½ pounds March 16-31, from 140 to 137 pounds

CASE 14—David K, aged 54, architect in reduced circumstances, admitted Feb 21, 1913, discharged March 26, 1913 Service of Dr Hartwell

Diagnosis Chronic interstitial nephritis Arteriosclerosis Inguinal hernia

Past History Three years previous to admission he noticed a small lump in his left groin There was little discomfort until two years later when it became painful Is very alcoholic

March 21, 1913 Four weeks ago the patient was operated on for inguinal hernia He now seems absolutely normal He was out on a pass yesterday and returned at 7 p m For breakfast he had a cup of coffee without sugar or milk

March 26, 1913 Heart apex neither visible nor palpable Left limit of dulness in the fifth space, 12.5 cm to the left of the midline Over the aortic area there is a rough systolic impurity of the first sound The second aortic sound is loud and ringing There is no enlargement to the right of the sternum The radials are palpable

March 26, 1913 Patient discharged

Urine Trace albumin

Blood Pressure March 26, systolic, 195, diastolic, 110

CASE 15—William A., aged 24, laborer, admitted Dec 28 1914, discharged Jan 30, 1915 Service of Dr Coleman

Diagnosis Aortic regurgitation

Complaint Pain in right side of chest Difficulty of breathing when lying down

Past History Has had measles, pneumonia and rheumatism Has had gonorrhea Tonsils have given him trouble Tonsils are enlarged

Present Illness Dec 25, 1914, he was taken with a very sharp pain in his side The following night he could not lie down He felt his heart beating He now feels weak and coughs a good deal

Physical Examination The patient is a well developed and well nourished young man 180 cm tall His tonsils are swollen and congested The cardiac impulse is seen in a diffuse area around the nipple and is forcible The upper border is in the third interspace, right border 4 cm from the midsternal line, left border 13 cm from the midsternal line There is a Flint murmur at the apex and also a diastolic murmur Corrigan pulse

January 11, 1915 Lungs are normal Patient is comfortable except for a slight cough The diastolic and Flint murmurs still continued There is a short systolic murmur at the apex

January 15 There is a blowing systolic murmur at the aortic region transmitted along the vessels of the neck and arm

January 26 The patient has been in a chair all day without fatigue He was examined upright in the chair The cardiac impulse was forceful, maximum in the fifth space The left limit of dulness in the fifth space, 13.5 cm from the midline in the fourth space 11.5 cm from the midline, right limit of dulness at the sternal margin In the aortic region there is a systolic murmur transmitted upward and a blowing diastolic murmur transmitted downward At the apex there is a short systolic murmur and a rumbling murmur in diastole Pulse of Corrigan type

Blood Pressure Systolic 140

Urine Clear, amber, specific gravity 1.030

Temperature Dec 31, 1914, to Jan 2, 1915 from 99 to 101 F Jan 6, 1915, varied slightly around the normal

Respiration From 18 to 20

Pulse From 65 to 80

Electrocardiogram "T" waves directed downward in the second and third leads In the calorimeter, Jan 25 and 27, 1915

CASE 16—Theodore S., aged 32, coachman, single, admitted Jan 17 1914, discharged Feb 22, 1914

Diagnosis Chronic cardiac valvular disease Cardiac hypertrophy and dilatation

Past History He had pneumonia at the age of 6 years In 1906 he had typhoid fever He has had no rheumatism At 8 years of age he was operated on for some abdominal condition He was a moderate user of beer, but for the last two or three years he has used none He stopped working one year ago In Sweden he did rough carpenter work one year Last year he was a driver

Present Illness For four or five years he has been short of breath, especially on exertion At times he has had a pain in his left side For one month he has had a short, sharp, hacking cough He sleeps well He was obliged to take an

easy job three years ago, as the doctor said he had heart trouble. Eight months ago he could carry a trunk upstairs. For two weeks he has been confined to the house.

**Physical Examination** The patient is of medium build, 169 cm tall, a well developed and well nourished man. Arteries are palpable. Sibilant râles at both bases.

Jan 19, 1914 Patient is quite comfortable, not dyspneic, slight cyanosis of the lips.

January 26 Condition excellent. Slight cough, no dyspnea, no orthopnea. Sat up in chair without fatigue. Apex beat in the fifth space, 12 cm from the midline, left limit of dullness in the fifth space 14.5 cm from the midline, in the fourth space 12.5 cm from the midline, right limit of dullness in the third space 3 cm from the midline, in the fourth space 4 cm from the midline. Heart action very slow, heavy, irregular in force and rate. Tracings show absence of the "A" wave, typical auricular fibrillation. At the apex the first sound is sharp and short. The second sound is faint. There is a loud, rough, rumbling murmur starting almost immediately after the second sound and diminishing in intensity during diastole, lasting throughout the short diastolic pauses, but stopping before the end of the long diastoles. At the base of the heart the pulmonary second sound is very much accentuated. The radial pulse corresponds with the apex impulse. The beats vary in size. Wall not palpable. There are a few sibilant and sonorous sounds in the lungs. No edema. Mucous membranes are deep red and slightly cyanotic.

February 10 The patient is up and about. He can walk up one and a half flights of steps.

February 11 The patient was given 1/120 grain atrophin, repeated after twenty-one minutes. Five minutes after the second dose the pulse rate increased from 48 to 55, the apex rate increased up to 96, and there was a large pulse deficit. At the apex the rate became almost regular, but not so regular in force. Throat dry, pupils dilated. The patient felt bad the next day, "As if he had been on a debauch."

February 15 The patient is sitting in a chair. Pulse 49, blood pressure, large beats, systolic, 145, diastolic, 85. After climbing stairs, pulse, 46, diastolic blood pressure, 150, systolic, 85.

February 21 Sounds as before. Wassermann negative.

Temperature January 17-27, from 98 to 100 F. From January 28 on, the temperature was normal.

Roentgenogram of heart

	Upright	Horizontal
Left	11.3	12.85
Right	8.35	7.8
	<hr/> 19.65	<hr/> 20.65

No medication.

The patient caught cold at home and was readmitted, March 4, 1914, with bronchopneumonia. Heart sounds the same. Discharged March 27, 1914.

# CLINICAL CALORIMETRY

## SEVENTEENTH PAPER

### METABOLISM AND TREATMENT IN DIABETES\*

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The experiments here to be described concern two patients with moderate diabetes treated by the oatmeal method in the metabolism ward of the Russell Sage Institute of Pathology and four Rockefeller Hospital patients with more severe diabetes transferred to Bellevue Hospital for study in the respiration calorimeter during various stages of the fasting treatment. Only very brief mention is possible of the literature<sup>1</sup> concerning the subjects touched upon in the experiments, namely, (1) the oatmeal and fasting treatment, (2) the dextrose-nitrogen ratio, (3) the respiratory quotient under certain conditions, and (4) the total metabolism in diabetes.

1 According to literature previously reviewed,<sup>2</sup> the von Noorden school no longer holds that oatmeal stands entirely alone in respect to the capability of utilization by diabetic patients, but nevertheless maintains that for some unknown reason it is superior to other forms of carbohydrate. On the other hand, Blum<sup>3</sup> and a series of later authors have been able to observe no difference in the clinical effects of oatmeal and other carbohydrates. Also von Noorden has claimed that cases of the worst type are the ones that do best on oatmeal, whereas in mild cases the method often fails. The opposing authors found that oatmeal, like other carbohydrates, was tolerated better in mild cases and worse in severe cases. Furthermore, even in the seemingly favorable cases where the carbohydrate balance is strongly positive, respiration experiments have usually shown little or no combus-

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1 A fuller review by one of the authors (F M A) is to be published elsewhere

2 Allen, Frederick M. *Studies Concerning Glycosuria and Diabetes*, Harvard University Press, Cambridge, Mass., 1913

3 Blum, L. *Les Hydrates de Carbone dans le Traitement du Diabète Sucré*, *Semaine Médicale*, 1911, xxxi, 313, *Ueber Weizenmehlkuren bei Diabetes mellitus*, *Beitrag zur Theorie der Verwendung der Kohlehydrate in der Therapie der Zuckerkrankheit*, *München med Wchnschr*, 1911, lviii, 1433, *Die Diät bei Diabetes gravis*, *Med Klin*, 1913, p 702

tion of carbohydrate. Thus Benedict and Joslin<sup>4</sup> concluded that the carbohydrate ingested produced no material effect upon the metabolism, and Joslin<sup>5</sup> shows the failure of either oatmeal or potato to raise the respiratory quotient, notwithstanding positive carbohydrate balances as high as 100 gm. Falta<sup>6</sup> states, without giving details, that a diabetic patient taking 400 gm oatmeal daily without glycosuria showed no rise in the respiratory quotient on the first or second days, but on the third day a marked rise in the quotient occurred. Normal persons showed the usual prompt rise in the quotient, but when subjected to the customary program of the "oat cure," namely, first a period of carbohydrate-free diet, then the customary fasting or vegetable-day, then a period of 400 gm oatmeal daily, a normal person showed the same behavior as the diabetic, in that the quotient rose only on the third day. The reason was believed to be that the organism, impoverished in carbohydrate, first stored the ingested starch as glycogen without burning any considerable quantity. The records of Rolly<sup>7</sup> and Roth<sup>8</sup> concerning the administration of different carbohydrates to diabetics show no appreciable changes in the quotients during the series of successive days in their experiments. Joslin<sup>9</sup> pointed out that the respiratory quotient of Benedict's fasting man rose promptly on taking mixed diet at the end of a thirty-one-day fast. Confirmation is necessary before it can be accepted that either a diabetic or a normal subject will store the carbohydrate of 400 gm oatmeal for two days, and then suddenly show active combustion on the third day. Any such change in the respiratory quotient of a diabetic patient would more probably indicate an improvement in the power of carbohydrate combustion.

Von Noorden and all other writers admit that many cases of diabetes are so severe that neither the glycosuria nor the acidosis is cleared up by the oatmeal treatment. The method recently introduced,<sup>9</sup>

4 Benedict, F. G., and Joslin, E. P. *Metabolism in Diabetes Mellitus*, Carnegie Institution of Washington, 1910, Pub. No. 136, pp. 203, 215, *A Study of Metabolism in Severe Diabetes*, Carnegie Institution of Washington, 1912, Pub. No. 176, *Ueber den Stoff- und Energieumsatz bei Diabetes*, *Deutsch Arch f klin Med*, 1913, cx1, 333.

5 Joslin, E. P. *Carbohydrate Utilization in Diabetes*, *THE ARCHIVES INT MED*, 1915, xvi, 693.

6 Falta, W. *Zur Theorie und Behandlung des Diabetes mellitus*, *Med Klin*, 1914, x, 9.

7 Rolly, F. *Zur Theorie und Therapie des Diabetes mellitus*, *Deutsch Arch f klin Med*, 1912, cv, 494.

8 Roth, N. *Ueber Mehltage bei Diabetes*, *Wien klin Wchnschr*, 1912, xxv, p. 1864.

9 Allen, Frederick M. *Studies Concerning Diabetes*, *Jour Am Med Assn*, 1914, lxiii, 939, *Boston Med and Surg Jour*, 1915, clxxii, 242, *New York State Jour Med*, 1915, xv, 330, *Am Jour Med Sc*, 1915, cl, 480, *Exercise*, *Boston Med and Surg Jour*, 1915, clxxiii, 743, *Investigative and Scientific Phases of the Diabetic Question, with Their Probable Relations to Practical Problems of Clinical Medicine*, *Jour Am Med Assn*, 1916, lxxvi, No. 20, p. 1525.

consisting of a prolonged initial fast with subsequent strict regulation of all elements of the diet, has proved successful in clearing up both the urinary and the clinical symptoms in a considerable number of cases, even of very severe diabetes. The underlying principles will be discussed more fully elsewhere, but one feature considered theoretically important for the beneficial results has consisted in a diminution in the metabolism, not merely of the sugar-forming materials (carbohydrate and protein) but also of fat. The question of diminution of metabolism could be settled only by experiments in the respiration calorimeter.

2 The first dextrose-nitrogen ratio was established by Minkowski, who discovered that totally depancreatized dogs, fasting or on carbohydrate-free diet, excreted in the urine approximately 28 gm of glucose for each gram of nitrogen. A constant ratio at this level indicates that 45 per cent of the protein catabolized is being formed into glucose and excreted, and that no sugar is being formed from fat. The original interpretation was furthermore that 45 per cent represents the maximum proportion of protein convertible into sugar. Lusk<sup>10</sup> and collaborators demonstrated that phlorhizined dogs eliminate approximately 3.65 gm of glucose for each gram of nitrogen, thus proving that at least some species of animals are capable of converting nearly 60 per cent of the protein molecule into glucose. Also, there is no formation of sugar from fat under these conditions. Mandel and Lusk<sup>11</sup> demonstrated the 3.65 ratio in a human patient with severe diabetes. They urged the prognostic value of determinations of the relations of sugar and nitrogen on carbohydrate-free diet, and because the total loss of power to use carbohydrate indicated by the 3.65 ratio supposedly precluded improvement, they referred to this as the "fatal ratio." Foster and Greenwald<sup>12</sup> also described cases showing this ratio. For other literature, reference may be made to Lusk.<sup>13</sup> Inasmuch as the case described by Allard showed a fall in the ratio on fast-days, Lusk considered it no longer certain that the 3.65 ratio is necessarily permanent or fatal.

10 Lusk, G. Phlorhizinglukosurie, *Ergebnisse der Physiologie*, 1912, *xii*, 315.

11 Mandel, A. R., and Lusk, G. Stoffwechselbeobachtungen an einem Falle von Diabetes mellitus, mit besonderer Berücksichtigung der Prognose, *Deutsch Arch f klin Med*, 1904, *lxxxv*, 472, *Diabetes Mellitus. Report on a Case, Including a New Method of Prognosis*, *Jour Am Med Assn*, July 23, 1904, p. 241.

12 Foster, N. B. Wie hoch ist der Dextrose Stickstoff-Quotient bei schwerstem Diabetes? *Deutsch Arch f klin Med*, 1913, *cx*, 501, Greenwald, I. *Jour Biol Chem*, 1913-14, *xvi*, 375, and 1914, *xviii*, 115.

13 Lusk, G. Metabolism in Diabetes, *THE ARCHIVES INT MED*, 1909, *iii*, v, Note on "A Case of Pancreatic Diabetes Mellitus," by Herman O. Mosenthal, *THE ARCHIVES INT MED*, 1912, *x*, 122. Allard *Arch f exper Path u Phar*, 1907 *lvii*, 1.

3 The level of the respiratory quotient theoretically to be expected in diabetes has been discussed by Magnus-Levy<sup>14</sup> and by Lusk<sup>15, 16</sup> On the basis of the newer information concerning the amino-acid content of proteins, the latter calculates that when the dextrose-nitrogen ratio is 3.65, the quotient of protein is 0.632 The formation and excretion of acetone bodies also tends to lower the quotient in a manner which can be calculated, but at the same time such acid substances may react with sodium bicarbonate to set free carbon dioxide, so that the precise theoretical value of the quotient in diabetes cannot be determined The actual observations in phlorhizimized dogs and human patients with the 3.65 ratio are found to meet the theoretical expectations with quotients approximating 0.69 Two features of the recent literature concerning the respiratory quotient require mention in the present connection One is the absence, in exact modern work, of the very low quotients previously found in diabetes and other conditions Leimdorfer<sup>17</sup> is the only recent author who reports such low quotients, and as they are so numerous in his experiments, while his cases of diabetes were obviously of no extraordinary severity, it is apparent that something in his methods tended to give low values Grafe and Wolf,<sup>37</sup> though reporting dextrose-nitrogen ratios indicating formation of sugar from fat, found no support for this hypothesis in the respiratory quotient, which was about 0.74 Technical errors, especially in connection with the oxygen measurements (Benedict<sup>18</sup>), may be assumed to explain the low values in the early literature The average quotient of Benedict and Joslin's severe cases of diabetes was 0.73, and Joslin<sup>5</sup> presents a table of the other cases in the literature, showing the general average to be 0.73 Respiration experiments therefore stand opposed to the doctrine of sugar-formation from fat in human

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14 Magnus-Levy, A. Respirationsversuche an diabetischen Menschen, *Ztschr f klin Med*, 1905, lvi, 83

15 Lusk, G. Clinical Calorimetry, Paper Eight. On the Diabetic Respiratory Quotient, *THE ARCHIVES INT MED*, 1915, xv, 939

16 Williams, H. B., Riche, J. A., and Lusk, G. Animal Calorimetry II. The Metabolism of the Dog Following the Ingestion of Meat in Large Quantities, *Jour Biol Chem*, 1912, xii, 349, 356

17 Leimdorfer, A. Ueber den respiratorischen Stoffwechsel des Diabetikers bei verschiedener Kostform, *Biochem Ztschr*, 1912, xl, 326

18 Benedict, F. G. A Comparison of the Direct and Indirect Determination of Oxygen Consumed by Man, *Am Jour Physiol*, 1910, xxvi, 15, Factors Affecting Basal Metabolism, *Jour Biol Chem*, 1915, xx, 263, Metabolism During Inanition, *Harvey Lectures*, 1906-07

Benedict, F. G., and Emmes, L. E. The Basal Gaseous Metabolism in Men and Women, *Jour Biol Chem*, 1914, xviii, 139, A Comparison of the Basal Metabolism of Normal Men and Women, *Proc Nat Acad Sc*, 1915, i, 104, A Comparison of the Basal Metabolism of Normal Men and Women, *Jour Biol Chem*, 1915, xx, 253, Benedict, F. G., and Smith, H. M. The Metabolism of Athletes as Compared with Normal Individuals of Similar Height and Weight, *Jour Biol Chem*, 1915, xx, 243



diabetes. The second feature to be mentioned consists in the unexpectedly high quotients shown by some cases of severe diabetes, as observed independently by Benedict and Joslin and by observers in the Russell Sage laboratory. Table 5 in the paper by Joslin<sup>19</sup> contains the record of a patient with severe diabetes, fasting except for from 2 to 5 gm protein and from 15 to 24 gm alcohol daily, yet with respiratory quotient of from 0.74 to 0.76. Joslin<sup>19</sup> mentions other observations of a rise in the respiratory quotient of severely diabetic patients during fasting, even up to the neighborhood of 0.8. The cause of such high quotients is not known. Nothing analogous has been described in the study by Benedict<sup>20</sup> and earlier workers of cases of prolonged fasting; they found that in normal persons the quotient falls and remains low during fasting. Aside from the presumably scanty supply of stored carbohydrate, Joslin has suggested the acetone bodies as the only known material capable of raising the quotients of diabetic patients by combustion under these conditions.

4. The total metabolism in diabetes has been an actively discussed subject. The earlier literature is critically reviewed by Benedict and Joslin.<sup>1</sup> It has been universally agreed that the basal metabolism of mild cases of diabetes is normal, and that of most severe cases is found increased when reckoned per kilogram of body weight. But in addition to accuracy in measuring the gas exchange and heat production, there is the further requirement of an accurate basis of comparison between diabetics and other persons. Magnus-Levy<sup>14</sup> called attention to the fact that the emaciation of most patients with severe diabetes alters the relation of their body weight and surface, and suggested that it might be more nearly correct to compare on the basis of the original normal weight of the diabetics. Benedict and Joslin rejected this proposal, because the surface of the diabetic apparently diminishes with the body mass and the skin shows no tendency to fall in folds or wrinkles. They chose, as the most accurate means available, to compare groups of patients with severe diabetes with groups of normal and mildly diabetic persons, as nearly like them as possible in size and figure. On this basis they estimated that their severely diabetic patients showed an increase of from 6 to 7 per cent in carbon dioxide excretion, of from 16 to 21 per cent in oxygen consumption, and of about 15 per cent in heat production. Lusk<sup>21</sup> criticized the findings in various particulars, and by recalculation concluded that the metabolism

19 Joslin, E. P. *Present-Day Treatment and Prognosis in Diabetes*, Am Jour Med Sc, 1915, cl, 485.

20 Benedict, F. G. *The Influence of Inanition on Metabolism*, Carnegie Institution of Washington, 1907. *A Study of Prolonged Fasting*, Carnegie Institution of Washington, Pub No 203, 1915.

21 Lusk, G. *Science*, 1911, N. S., xxxiii, 433-434.

represented was not 15 per cent but only 5 per cent above normal Benedict and Joslin<sup>4</sup> in their second publication added to the number of diabetics and especially of control subjects studied, and reckoned that the basal metabolism in this group of diabetics was approximately 20 per cent above normal Lusk<sup>22</sup> calculated that an increase of from 5 to 10 per cent, and in exceptional instances 15 per cent, above normal was shown Leimdorfer<sup>17</sup> found an increase of metabolism in severe cases of diabetes on the basis both of the weight and of the body surface as figured by Meeh's<sup>23</sup> formula Diminution of metabolism observed after oat or vegetable days was held to confirm this interpretation Rolly<sup>7</sup> found in severe diabetes an increased oxygen consumption per kilogram of body weight, especially soon after admission to hospital, after a period of treatment the findings were lower Seib<sup>24</sup> also reported the respiratory metabolism increased in proportion to the severity of the case In Paper 10 of the present series is described the height-weight formula for calculating the body surface, which has been found more accurate and reliable for this purpose than the Meeh formula, especially when the body form varies in any way from the average normal It is possible by this formula to recalculate any results recorded in the literature, wherever the height and weight of the subject have been given It is believed that the second of the requirements mentioned is thus fulfilled, and that, granting accurate experimental observations, a correct basis of comparison is afforded between diabetic and other subjects in a manner not possible heretofore

The causes of the departure of the diabetic basal metabolism from the normal are partly known, perhaps partly unknown It may be taken as an axiom that the diabetic, excreting sugar formed from protein, must catabolize more protein during fasting than the nondiabetic person under identical conditions, and that the specific dynamic action of protein will therefore give rise to a higher metabolism in the diabetic, unless some other factor prevents or neutralizes the effect of the protein The suggestion was offered by Benedict and Joslin that acidosis may be a cause of increased metabolism They observed the discrepant fact that a sudden slight acidosis is accompanied by an increase of metabolism out of proportion to that noted with prolonged high acidosis At the present time the subject of acidosis is a confused one,

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22 Lusk, G. *Animal Calorimetry XI. An Investigation into the Cause of the Specific Dynamic Action of the Foodstuffs*, Jour Biol Chem, 1915, xx, 555

23 Meeh, K. *Oberflächenmessungen des menschlichen Körpers*, Ztschr f Biol, 1879, xv, 425

24 Seib, K. *Experimentelle Untersuchungen über den respiratorischen Gasaustausch bei Diabetes mellitus nach Eiweisszufuhr und bei Hyperthermie*, Zentralbl f Physiol, 1913-14, xxvii, 930

it can no longer be regarded as a simple condition resulting from lack of carbohydrate.<sup>25</sup> Greater clearness concerning the effect upon metabolism may now result from separate consideration of individual factors present. First, some or all cases of sudden acidosis are accompanied by increased protein breakdown, which may be a cause of increased metabolism. Second, if acidosis in the strict sense increases metabolism, not only should subjects with high acidosis show higher metabolism than those with low acidosis, but also alkali given in sufficient quantity should in suitable cases cause a fall in metabolism. Third, it is possible that acetone bodies, even in the form of neutral salts, may stimulate metabolism if present in excess in the blood and tissues. Here the suggestion is analogous to that of Lusk<sup>25</sup> that diabetic lipemia may be a cause of increased metabolism. Increased concentration of combustible materials may be expected to result in a stimulation of metabolism, unless the power of combustion is diminished, or the specific dynamic action otherwise prevented. At the same time, the narcotic and depressant action of the acetone bodies might conceivably tend to depress metabolism, especially in the long-standing cases with high ketonemia. Other influences unquestionably tend to depress metabolism in such cases, as for example undernutrition and muscular relaxation. The effect of muscular mass and tone is evident in the higher metabolism of men as compared with women, and of athletes as compared with other men (Benedict<sup>18</sup> and collaborators), and Lusk<sup>22</sup> has shown that mere prolonged cage life may reduce a dog's basal metabolism by 16 per cent, though the diet and weight remain the same. The subject will be further considered below.

An account of the metabolism in a case of diabetes of remarkable intensity was recently published by Geyelin and DuBois.<sup>26</sup> To facilitate reference, some of the findings in this case are briefly reproduced in Table 1.

#### METHODS AND CALCULATIONS

The procedures used for the chemical determinations were as follows: for the blood-sugar, the method of Lewis and Benedict,<sup>27</sup> for the urinary sugar, titration with Benedict's solution, for nitrogen, the usual Kjeldahl method, for ammonia, the Folin method, for acetone bodies, the Shaffer method. Foods were weighed raw and the composition estimated from the Atwater-Benedict tables, unless special mention is made of analyses. For separating the twenty-four-hour urines,

<sup>25</sup> Lusk, G. The Influence of Food on Metabolism, *Proc. Am. Soc. Biol. Chem.*, December, 1914, *Jour. Biol. Chem.*, 1915, **xx**, 8.

<sup>26</sup> Geyelin, H. R., and Du Bois, E. F. *Jour. Am. Med. Assn.*, 1916, **lxvi**, No. 20, 1532.

<sup>27</sup> Lewis, R. C., and Benedict, S. R. A Method for the Estimation of Sugar in Small Quantities of Blood, *Jour. Biol. Chem.*, 1915, **xx**, 61.

TABLE 1—JUL CASL OF CYRIL K (SUMMARY FROM GUYLIN AND DUBOIS)

Date	Food				Urine				Respira tory Quotient	Calories per Sq. M. per Hour Linear Formula	Blood	
	Total Calories	Fat, Gm	Nitrogen, Gm	Carbo- hydrate, Gm	Nitrogen, Gm	Glucose, Gm	Dextrose Nitrogen Ratio	Beta oxy- butyric, Gm			Glucose, Mg per 100 c c	CO <sub>2</sub> Combining Capacity, mm
Dec 8 9	118*	0	0	0	27.9	71.9	2.68	13.8			313	30.1
Dec 9 10	336*	0	0	0	29.8	78.3	2.61	11.6				
Dec 10 11	0	0	0	0	21.8	71.2	2.95				310	26.6
Dec 11 12	105	17.7	2.8	11.5	30.6	108.0	2.17	60.0			312	24.1
Dec 12 13	1,058	69.6	8.0	50.0	31.5	112.0	1.80	53.0				22.7
Dec 13 14	938	58.5	8.8	50.0	35.1	118.7	1.03	37.9				22.5
Dec 14 15	930	51.2	9.8	53.3	37.7	118.5	1.73	55.2				
Dec 15 16	931	11.0	19.0	23.5	36.1	167.9	3.97	70.9	0.687	15.7†		20.0
Dec 16 17	158	5.6	15.9	0.1	38.3	153.1	1.01	75.1	0.711	12.6†		19.6
Dec 17 18	191	2.9	6.3	0.1	36.3	110.3	3.87	87.1			150	35.1 35.1
Dec 18 19	0	0	0	0	20.0	55.1	2.76	58.5	0.707	10.8		
Dec 19 20	0	0	0	0	16.7	11.3	2.65	56.8				19.7
Dec 20 21	36	0	1.6	1.0	11.1	35.3	2.11	11.2	0.721	37.0	177	52.5
Dec 21 22	60	0	3.2	1.6	11.1	39.7	2.65	26.2			170	
Dec 22 23	80	0.1	3.1	5.6	18.3	26.0	1.12	11.0	0.731	35.9	181	52.9
Feb 16						0	0	0	0.915	25.1		

\* Alcohol

† After breakfast, not basal

patients emptied the bladder at precisely 5 a. m. daily, and care was taken that no urine was lost under any conditions. The entire planning and organization of the ward was for the purpose of exact metabolic studies, and accuracy in matters of dietary control, collection of excreta and other details is fully assured.

At the time of the diabetes experiments the calorimeter was in perfect working order and the staff was well trained. Alcohol checks lasting two or three hours gave respiratory quotients in which even the third decimal place was not far from the theoretical. In experiments on man it has never before been felt advisable in this laboratory to print more than two significant figures in the respiratory quotients, but it has seemed justifiable to use three in the present work, both on account of the extreme care in the experiments and of the importance of the third decimal point in some of the calculations. In no case are deductions made from single hours but only from the averages of periods as long as possible.

The calculations concerning the metabolism where there was sugar formation from protein followed the method described by Lusk<sup>10</sup>. In the normal metabolism each gram of nitrogen in the urine indicates the combustion of 6.25 gm. protein with the liberation from this protein of 26.51 calories, 9.35 gm. carbon dioxide and the absorption of 8.45 gm. oxygen. It is obvious that if part of this protein molecule is unoxidized in the diabetic organism and is excreted in the urine, all of these figures will be lowered by exactly the number of calories and grams of carbon dioxide and oxygen lost in the glucose. With a dextrose-nitrogen ratio of 3.65 to 1, 1 gram of nitrogen in the urine indicates the combustion of 6.25 gm. protein with the liberation of 26.51 minus 13.47 calories, 9.35 minus 5.35 gm. carbon dioxide, and the absorption of 8.45 minus 3.89 gm. oxygen. When the dextrose-nitrogen ratio is lower, the calculation is easily made as follows. The calories, carbon dioxide and oxygen ascribed to the metabolism of protein are calculated from the number of grams of nitrogen excreted per hour by using the normal factors given by Lusk<sup>10</sup>. Knowing the number of grams of glucose excreted per hour, one can make the proper subtractions, since each gram of glucose represents a loss of 3.692 calories, 1.467 gm. carbon dioxide and 1.067 gm. oxygen. In this way it is possible to determine the nonprotein respiratory quotient and the heat production by the method of indirect calorimetry. If there is no glycosuria, or if the sugar of the urine is all derived from ingested carbohydrate, the calculations are exactly the same as for normal persons. No attempt has been made to calculate the combustion of the acetone bodies or the ingested alcohol, the conditions of experimentation rendering this impossible.

For reasons fully stated in previous papers, the method of indirect calorimetry is used as the standard, and the divergence of the direct calorimetry from this is expressed in terms of percentage. In typhoid fever, exophthalmic goiter, anemia and cardiorenal disease there is a tendency for the direct calorimetry to average from 2 to 3 per cent lower, probably on account of heat lost through the warming of the bed and clothing, possibly also because of errors in measuring the average temperature of the body. This same tendency to a small minus error is seen in most of the diabetes experiments. The total divergence of the two methods in the present work is 2.3 per cent, and the average

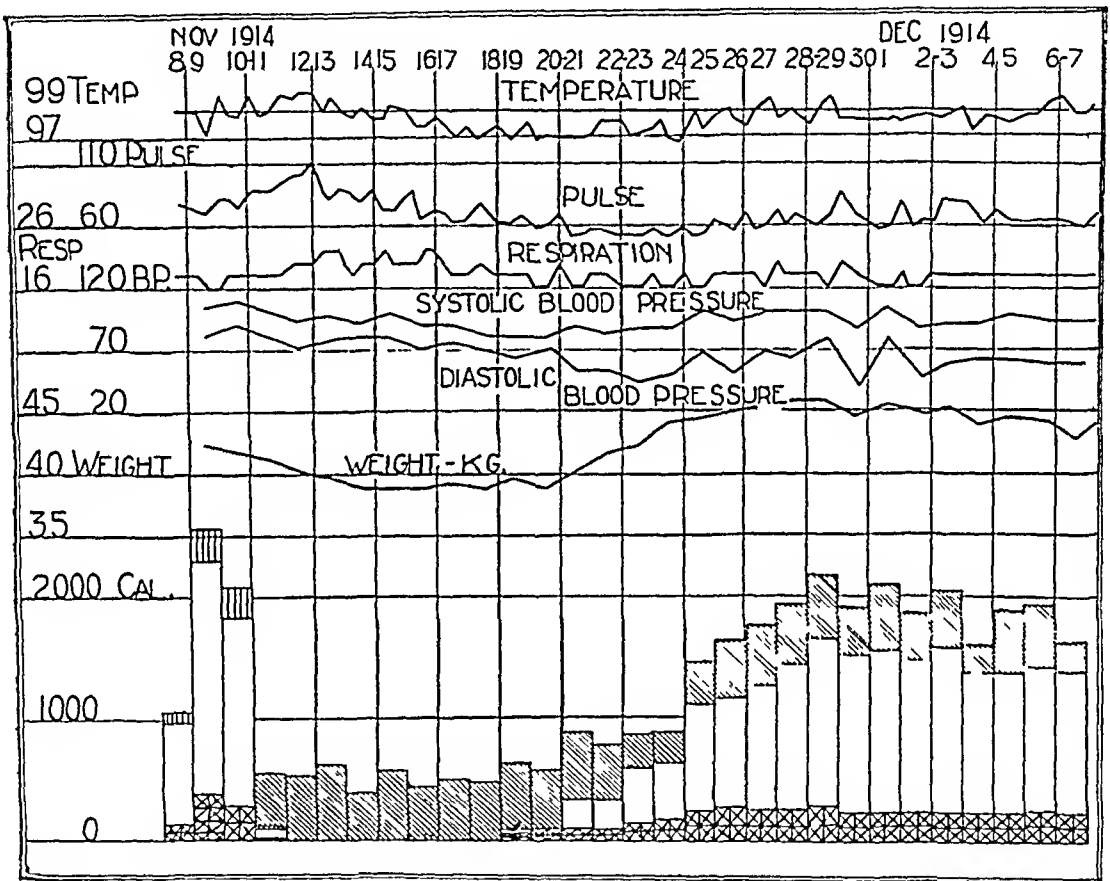


Fig 1 (Gerald S) —Clinical findings shown graphically. The columns at the base represent the calories of the food, vertical lines, carbohydrate, crossed lines, protein, diagonal lines, alcohol, blank space, fat calories.

divergence in individual experiments is plus or minus 5.5 per cent. The agreement of the two methods is therefore satisfactory, and would be still closer but for the peculiar divergence of the findings in the case of Gerald S. on the last day of the prolonged fast and during the following two weeks. This point is discussed in the history of his case, which follows.

#### CASE REPORTS

CASE 1—Gerald S. (severe diabetes), plumber, aged 17, unmarried. Healthy family and past life, habits good, normal weight 60 kg. Polyuria and polydipsia were noticed January, 1914. Entered Bellevue Hospital June, 1914, weighing

TABLE 2—GIRALD S —

Date, 1914	Food						Urine N, Gm	Urine Glucose, Gm
	Total Calories	Protein, Gm	Fat, Gm	Carbo., Gm	Alcohol, Gm	Food N, Gm		
Nov 8 9	1,056*	41.2	91.7	18.3		4.69		
Nov 9 10	2,550	96.2	204.4	62.2		15.40		
Nov 10 11	2,078	67.0	166.4	62.1		10.72	14.71	106.43
Nov 11 12	540	1.3	9.5	2.3	12.6	0.20	10.76	41.95
Nov 12 13	526	0	0	0	7.2	0	10.40	24.49
Nov 1 14	614	0	0	0	87.7	0	10.87	15.68
Nov 14 15	80	0	0	0	4.3	0	9.0	8.91
Nov 15 16	500	0	0	0	7.0	0	11.10	6.53
Nov 16 17	1.8	0	0	0	12.6	0	8.52	7.10
Nov 17 18	497	0	0	0	71.0	0	8.24	2.89
Nov 18 19	408	0	0	0	14.8	0	6.11	0.76
Nov 19 20	622	12.2	1.8	2	70.3	1.05	7.12	0
Nov 20 21	578	14.5	2.4	2	71.0	2.32	5.72	0
Nov 21 22	892	24.1	25.8	2	70.3	3.85	8.41	0
Nov 22 23	787	21.0	25.1	2	66.8	3.36	6.45	0
Nov 23 24	876	34.6	47.7	2	41.8	5.53	9.13	0
Nov 24 25	887	37.6	50.5	2	37.6	6.01	7.23	0
Nov 25 26	1,464	57.0	97.0	3	50.1	9.26	6.56	0
Nov 26 27	1,635	65.7	95.6	2	71.0	10.51	8.20	0
Nov 27 28	1,552	61.1	110.8	2	71.0	9.77	7.17	0
Nov 28 29	1,929	61.1	130.0	2	71.0	9.77	7.18	Trace
Nov 29 30	2,175	68.4	141.5	2	75.0	10.75	8.58	Trace
Nov 30 Dec 1	1,797	56.0	140.6	2	41.8	8.96	6.89	Trace
Dec 1 2	2,077	55.1	146.7	2	75.2	8.81	6.73	1.71
Dec 2 3	1,815	57.3	138.9	2	50.1	9.16	5.72	0
Dec 3 4	2,034	55.7	148.1	2	66.8	8.91	5.94	Trace
Dec 4 5	1,606	53.9	126.6	2	33.4	8.62	5.49	0
Dec 5 6	1,893	53.4	126.2	2	75.2	8.54	7.23	0
Dec 6 7	1,912	56.0	130.0	2	75.2	9.10	6.80	0
Dec 7 8	1,614	54.4	127.2	2	33.4	8.70	6.61	0
Dec 8 9	1,872	56.4	128.9	2	66.8	9.02	6.95	0
Dec 9 10	2,022	56.2	146.6	2	66.8	8.99	6.56	0
Dec 10 11	2,111	54.8	145.0	2	66.8	8.76	7.28	0
Dec 11 12	2,191	52.9	166.0	2	66.8	8.46	7.06	0
Dec 12 13	2,308	60.0	175.6	2	66.8	9.60	7.73	0
Dec 13 14	2,208	61.1	164.3	2	66.8	9.77	7.17	0
Dec 14 15	2,221	59.2	166.6	2	66.8	9.74	6.22	0
Dec 15 16	2,368	68.4	172.1	2	75.2	10.94	7.45	0
Dec 16 17	2,532*	46.4	211.9	2	58.5	7.49		

\* Not complete

—CLINICAL DATA

Urine NH <sub>3</sub> , Gm	Beta oxy- butyric, Gm	Total Acetone Bodies as Beta oxybutyric Gm	Feces N,† Gm	Excreta N, Gm	Nitrogen Balance, Gm	Water Intake, Gm	Urine Volume, c c	Body Weight, c c	Blood Sugar, Per Cent
						1,450	1,300		
?						2,220	?	42 19	
3 40	7 128	13 218		15 78	— 1 07	2,060	3,326		
4 75	2 071	3 811	0	10 76	—10 75	3,705	3,460	41 27	0 305
4 46	1 815	2 517	0	10 40		2,398	1,909	40 15	
3 68	0 594	0 990	0			2,065	2 700	39 86	
2 18	0 616	1 048	0			2,197	1,836	38 97	
1 50	0 475	1 155	0			2,450	2,563	38 92	0 286
0 90	0 416	0 656	0			1,570	1,428	38 80	
0 71	0 308	0 588	0			2,385	2,128	39 05	0 284
0 60	0 064	0 164	0			1,725	1,153	38 74	
0 57	0 436	0 592	0 234	7 35		2,685	3,115	39 55	0 198
0 42	0 186	0 322	0 29	6 01		2,185	1 980	38 74	
0 51	0 208	0 373	0 46	8 87		2,883	2,360	40 22	
0 48	0 341	0 613	0 40	6 85		2,375	1,940	41 87	0 156
0 49	Lost		0 66	9 79		2,235	1 643	42 66	
0 56	0 258	0 423	0 72	7 95		1,500	1,835	44 02	0 182
0 44	0 250	0 358	1 11	7 49	+ 1 77	1,550	1,200	44 14	
0 68			1 11	9 31	+ 1 20	2,500	3 540		
0 46			1 11	8 28	+ 1 49	2,450	3,220	45 15	
0 50			1 11	8 29	+ 1 48	2,175	2,955	45 64	0 161
0 58			1 11	9 69	+ 1 06	2,780	4,005	45 27	
0 46			1 11	8 00	+ 0 96	1,870	2,225	44 27	
0 82			1 11	7 84	+ 0 97	1,795	3,085	45 35	0 208
0 38			0 945	6 67	+ 2 49	2,100	2,473	44 76	
0 55			0 945	6 885	+ 2 025	2,500	3,815	45 42	
0 30			0 945	6 435	+ 2 185	2,050	3,178	43 94	
0 57			0 95	8 18	+ 0 26	2,980	4,525	44 77	
0 44			0 95	7 28	+ 1 82	2,875	3,980	43 82	0 177
0 38			0 95	7 56	+ 1 14	1,455	2,327	42 58	
0 52			0 95	7 90	+ 1 12	2,010	3,610	43 32	
0 35			1 34	7 90	+ 1 09	3,070	3,750	42 61	
0 55			1 34	8 62	+ 0 14	3,000	3,880	41 74	
0 49			1 34	8 40	+ 0 06	3,250	3,865	42 43	
0 68			1 34	9 07	+ 0 53	2,510	3,110	42 30	
0 75			1 34	8 51	+ 1 26	2,730	3 010	42 36	0 113
0 60			1 34	7 56	+ 2 18	2,850	3,650	42 55	
0 71			1 34	8 79	+ 2 15	2,800	3,030	41 79(?)	
						2,605	1,565	42 67	

† Feces N calculated as 12% of Food N, up to November 26



47 kg. After twenty-five days he was discharged weighing 57 kg. Glycosuria was said to have been 10 per cent on admission, 5 per cent on discharge. A dose of salts taken October 24 left him very weak, and thereafter he lost weight and strength rapidly. He was admitted to Rockefeller Hospital Nov 7, 1914. Height 172 cm, weight 41.6 kg, extremely weak. Heart, lungs and abdomen negative, blood-pressure 85 systolic, 75 diastolic, clinical picture of acidosis, with drowsiness and increased respiration threatening coma. His diet containing

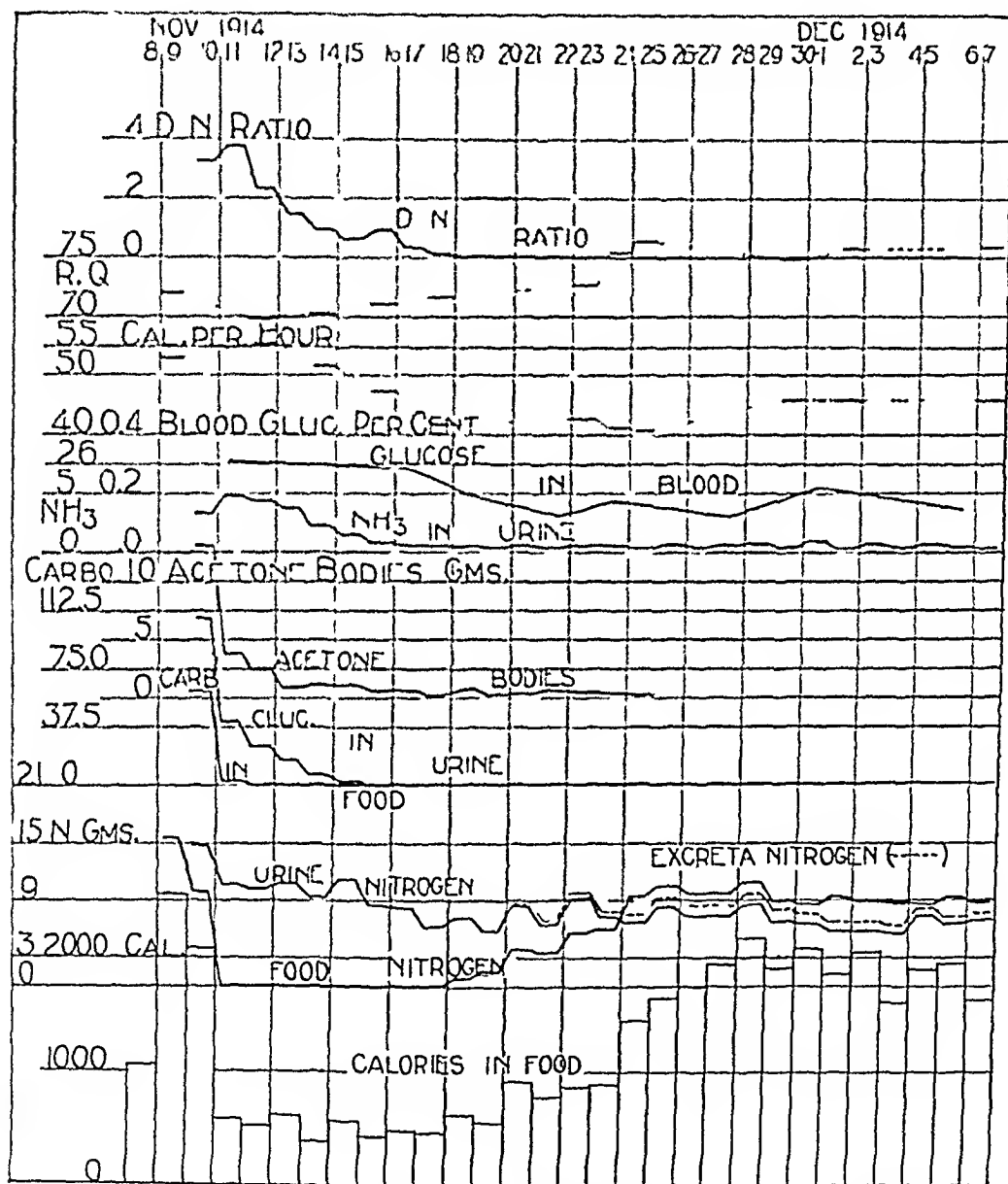


Fig 2 (Gerald S) —Laboratory findings shown graphically

carbohydrate was continued, and he was transferred next day to the Russell Sage metabolism ward at Bellevue Hospital, where he remained until the close of the metabolism experiments, then returned to the Rockefeller Hospital.

The diet shown in Table 2 was all he could eat on November 8 to 10 inclusive. At 6 a. m. on November 11 he received 50 cc cream, then developed nausea without vomiting. Fasting was begun at this time because of the complete repugnance to food and the dangerously threatening coma symptoms. No bicarbonate was given except 10 gm on November 11. The fast lasted eight days,

and the condition cleared up, as shown in the table. Alcohol was given in the form of whisky during the fast, in quantities just short of producing any discomfort or intoxication symptoms. Notwithstanding the extreme initial weakness, the clinical condition perceptibly improved during the fast. The first food added to the alcohol after the fast was protein—eggs at first, later meat. More protein and fat were gradually added, until the unduly high diet of over fifty calories per kilogram of weight was reached. Bulk was contributed to the diet by the use of from 750 to 1,000 gm of thrice-boiled vegetables daily, some samples of which were analyzed for carbohydrate. The rapid gain in weight shortly after the fast was due to the water retention common in such patients. Improvement continued in subsequent treatment. The carbohydrate tolerance remained low, but the patient became able to exercise freely, and he and his parents considered him fit for work. For this reason he refused to be further controlled, and was dismissed from the hospital and from all further supervision, with due warning of the consequences. The discharge was on Feb 8, 1915, the diet at that time being about 1,400 calories, with no glycosuria or ketonuria, and the body weight 44 kg. He progressed rapidly downward and died March 9, 1915.

CASE 2—William G (severe diabetes), printer, age 29, married. Family, personal history and habits negative. Figure thin, normal weight from 66 to 69 kg. Thirst and dry mouth noticed in June, 1913. Progress was steadily downward in spite of treatment. Entered Presbyterian Hospital July 25, 1914. His condition there was dangerous on carbohydrate-free diet and worse when it was attempted to add carbohydrate. The dextrose-nitrogen ratio was found to be about 3. He was transferred to Rockefeller Hospital on July 28. Height 179 cm, weight 50 kg. Physical examination negative. Table 3 contains part of the laboratory data for this period. Carbohydrate of food was determined only by calculation. Other food values for the first two days are calculated. After that, nitrogen and fat were analyzed in food and feces.

Thus the emaciated patient, spending most of the twenty-four hours in bed and the rest of each day sitting limply in a chair, was unable to maintain his body weight even on utilizable calories in excess of the needs of a normal person of equal weight. The excess of fat failed to prevent nitrogen loss. Yet high protein feeding is known to aggravate diabetes, even though temporary nitrogen equilibrium is attained. This is the old dilemma. As soon as the appetite partly failed, on August 1, the nitrogen deficit became large. Fasting had to be inaugurated on August 2 because of symptoms of beginning coma. Along with the fall in glycosuria, within two days the level of nitrogen excretion characteristic of advanced inanition was attained. Feeding with green vegetables was commenced August 7. Gradual increase of vegetables up to August 12 showed a carbohydrate tolerance of 38.5 gm. Other food was then given, and there seemed to be satisfactory improvement, with glycosuria and ketonuria absent as usual. The case then differed from others in that a gradual loss of tolerance manifested itself, diagnosis was impossible for several months, but the apparent explanation of the trouble was at length found in pulmonary tuberculosis. Vain attempts were made several times to increase strength by high feeding with disregard of glycosuria. In January, 1915, with no sign of tuberculosis, the patient spent some time in the Russell Sage metabolism ward for investigation before and after such a period of high diet.

TABLE 3—WILLIAM G CLINICAL DATA DURING FIRST PART OF STAY IN THE ROCKEFELLER HOSPITAL.

Date	Body Weight, Kg	Water Intake, c c	Urine						Nitro gen Balance*	Food					So dium Bi carbo nate Gm	Cal cium Carbo nate, Gm
			Vol ume, c c	Acetone Bodies as Butyric Acid, Gm	Am monia Nitro gen, Gm	Dex trose Gm	Dex trose Nitro gen Ratio	Total Nitro gen, Gm		Carbo hydrate, Gm	Alco hol, Gm	Calor'ies				
												In Food	All ably†			
July 29 30	49.4	1,800	3,421	26.05	2.83	61.63	2.6	23.27	- 0.56	17.29	6.9		2407	2448.1		20
July 30 31	47.4	2,540	2,370	20.51	2.16	64.99	3.3	17.45	- 0.66	17.70	11.5		2139	2276		20
July 31 Aug 1	47.0	2,200	2,970	19.69	2.73	53.24	2.7	20.19	+ 0.79	21.73	7.7	20	2155	2502.6		20
August 1 2	47.4	2,810	3,165	33.62	3.18	60.46	2.1	21.76	-1.63	12.61	5.8	20	2509	2212		20
August 2 3	47.4	2,642	1,935	15.76	1.25	17.85	1.2	11.53	-15.71			102	2110	679		20
August 3 4	48.0	1,930	2,185	8.80	2.08	1.93	0.26	7.22				97	1825	729		20
August 4 5	48.1	1,870	1,810	2.17	0.41	2.01	0.31	5.69				80	2000	1213		20
August 5 6	48.2	2,092	2,815	2.09	0.83	0		7.01				102	2110	620.0		5
August 6 7	47.6	2,722	2,100	2.97	1.07	0		10.20				92	1110	522.2		
August 7 8	47.0	2,785	2,365	1.95	1.16	0		6.72	- 7.26	0.34	5.8		6103	750		
August 8-9	47.2	2,545	1,625	3.10	1.06	0		7.66	- 7.19	0.55	17.7	55	1886	126.2		

\* Average daily N in feces 0.876 gm

\* Average daily N in feces 0.876 gm

† Calories lost in urine and feces subtracted from calories of diet

(Table 4) He was subjectively and objectively so much better when kept free from glycosuria and ketonuria, that this was done nearly constantly until March 11, 1915. Then the course of the tuberculosis was becoming very rapid. Death occurred from diabetes and bronchopneumonic tuberculosis on March 22, 1915.

CASE 3—Joseph U (severe diabetes), manufacturer, aged 44, married. His family, personal history and habits were negative. Normal weight 75 kg. In 1907, loss of weight, and medical diagnosis of diabetes. At first kept free from glycosuria occasionally by treatment, but it has been continuous for the past three or four years. Emaciation and weakness have been the principal symptoms. Patient was bedridden for the six weeks preceding admission to hospital. He was brought on a cot from his home in Indiana and entered Rockefeller Hospital Nov 28, 1914. Height 179 cm, weight 44.2 kg. Physical examination was negative, except for emaciation and a yellow tinge like pernicious anemia, which diagnosis was excluded by blood examination. Blood pressure not certain. On January 18, when he appeared much stronger and was beginning to sit up a little, systolic blood pressure was 76, diastolic 60. Glycosuria and ketonuria heavy. Ammonia nitrogen 2.5 gm on November 28-29, 2.78 gm on November 29-30. No symptoms of acidosis.

Treatment was conducted by Dr Stillman. The patient fasted November 30 to December 7, inclusive, receiving 70 cc whisky daily, and on December 7 receiving also 500 gm thrice-boiled vegetables. Eggs and butter were added gradually until on December 10 the diet contained 52 gm protein, 95 gm fat, 100 cc whisky, and 500 gm thrice-boiled vegetables. On this day a glycosuria of 9.5 gm appeared. The strength and well-being had improved from the outset, but though ketonuria had diminished, it had never cleared up satisfactorily. The carbohydrate tolerance was literally nothing. Details will be published elsewhere. Briefly, it was necessary to keep him on a diet of about 700 calories daily, about half of which was alcohol, until February 3. He was warm and quiet in bed except for short daily periods. The weight on February 3 was 40.3 kg, and strength continued to improve. It was toward the close of this prolonged undernutrition that the calorimeter tests were made, on January 31 and February 1. It then became possible to increase the diet somewhat, but fast-days were still used frequently. The ferric chlorid reaction slowly diminished to traces, but did not become regularly negative until the latter part of May. The patient was discharged June 28, 1915, at precisely his initial weight, namely, 44.2 kg, with urine normal on a diet of 80 gm protein, 15 gm carbohydrate and 1,950 calories. He has since conducted his business. Carelessness with his diet brought back glycosuria and required his return to the hospital on Oct 17, 1915, but the condition was much more favorable than before and the tolerance higher on discharge from the hospital this time (Jan 18, 1916) than on the previous occasion.

CASE 4—Edward M (moderately severe diabetes), customs inspector, aged 34, married. His family, personal history and habits were negative, except for chronic indigestion and constipation since the age of 22. Normal weight 80 kg. In July, 1913, occurred sudden attack of dizziness, colic, vomiting and diarrhea, with fever for one day. From that time on he was constantly thirsty and lost weight and strength. Diabetes diagnosed in September. Under inefficient treatment he was sugar-free for only two periods of one week each. Entered Rockefeller Hospital July 15, 1914. Weight 60.4 kg. Highly neurasthenic, but no serious emaciation or acidosis. Physical examination negative except for sallow color and enlarged liver. On restricted diet there was marked ketonuria and a negative carbohydrate balance of about 12 gm. Four days of fasting from July 18 to 21, inclusive, were required to stop glycosuria. Feeding was begun on July 23, with vegetables containing 12.2 gm carbohydrate

TABLE 4—WILLIAM G. CLINICAL DATA DURING STAY AT BELLEVUE HOSPITAL JANUARY 10 TO 15

Date	Body Weight, kg	Water Intake, c c	Urine						Nitrogen Balance	Food			
			Volume, c c	Diacetic Acid	Ammonia Nitrogen, Gm	Dextrose, Gm	Dextrose Nitrogen Ratio	Total Nitrogen, Gm		Nitrogen, Gm	Carbohydrate, Gm	Alcohol, Gm	Chloride
Jan 10 11	43.3	2,130	1,465		1.45	0		5.23	-0.17	5.5		7.1	1.775
Jan 11 12	43.2	1,910	1,177	++	1.60	0		6.17	+1.14	9.73	0.6	0.6	2.016
Jan 12 13	43.3	2,650	1,995	++	2.51	11.4	1.27	9.19	+1.13	10.63	0.6	7.4	2.461
Jan 13 14		2,350	2,520	++	2.76	15.3	2.02	7.18	+1.79	10.12	0.6	5.4	2.276
Jan 14 15	44.9	3,100	3,665	++	1.05	23.0	2.3	9.63	-1.73	12.91	1.0	57.4	27.8
Jan 15 16*	44.0	1,150	876		1.18	9.9	3.93	2.12		1.41	0.1	11.5	6.2
Jan 16 17	42.8	1,150	2,500	++		13.8	3.14	13.91	-	11.3		20.0	1.511
Jan 17 18	42.0	1,335	2,770	++	3.40	42.8	3.10	13.52	-0.19	12.68		0.0	2.335
Jan 18 19	40.8	750	2,775	++		16.7	3.11	13.39	-2.16	12.08		22.5	2.183
Jan 19 20	40.6	1,850	2,925	++		60.6				11.1	2.2	0.0	2.79
Jan 20 21		2,700	1,385	++		76.7	3.52	20.1	-6.51	14.29		0.0	2.55
Jan 21 22	42.4	4,030	1,700	++		15				15.15	2.2	22.5	2.768
Jan 22*	43	2,000	1,390	++		8.8	1.15	2.91	-2.51			10.0	2.80

\* Incomplete

† Only for the calorimeter periods

TABLE 5—FELIX K CLINICAL DATA

Date	Total Calories	Fat, Gm	Carbo, Gm in Food	Glucose, Gm in Urine	N in Food, Gm	N in Urine, Gm	Body Weight, kg	Urine Volume, c c	Remarks
1/14/14	2,046	155.4	57.7	12.05	14.2	12.13		820	
1/15/14	2,016	145.4	62.5	21.50	15.8	18.61	.	1,000	
1/16/14	2,092	163.0	62.4	12.50	12.5	12.61		920	
1/17/14	1,989	141.6	64.3	13.80	15.6	14.79	56.51	1,180	
1/18/14	2,304	177.7	58.2	10.00	16.0	15.19		1,300	
1/19/14	2,085	149.0	64.3	6.15	16.9	11.99	56.33	940	
1/20/14	1,964	140.1	62.9	0	15.6	15.52		1,580	
1/21/14	2,369	181.8	59.8	9.65	16.5	16.08	57.52	1,380	
1/22/14	2,667	216.4	60.4	9.11	15.8	12.16	56.52	1,170	
1/23/14	2,852	236.5	59.8	5.88	15.9	13.90		1,360	
1/24/14	2,684	218.5	59.8	8.08	15.9	12.39	57.07	1,300	
1/25/14	3,138	247.4	59.8	5.68	16.0	10.31		1,040	
1/26/14	2,733	173.7	59.8	7.14	16.1	11.77	56.76	1,360	
1/27/14	2,773	178.3	60.0	8.70	15.9	10.54		1,200	
1/28/14	3,059	183.3	59.8	5.88	16.0	12.33	57.01	1,120	
1/29/14	921	76.7	20.8	0	4.7	9.36		1,330	
1/30/14	2,986	179.9	60.5	0	16.2	13.84	56.98	1,460	
1/31/14	3,458	180.0	59.7	0	16.1	13.28		1,520	
2/ 1/14	3,492	182.1	61.9	Trace	16.5	13.84		1,600	
2/ 2/14	3,488	182.8	60.5	0	16.2	14.01	57.97	1,910	
2/ 3/14	3,492	203.8	60.5	6.88	16.2	12.95		2,220	
2/ 4/14	3,579	192.2	60.5	8.08	16.5	11.77	58.76	1,860	
2/ 5/14	3,580	192.2	60.7	5.68	16.3	11.54		1,640	
2/ 6/14	3,615	197.3	60.5	0	15.9	10.65		1,400	
2/ 7/14	3,663	201.5	59.7	6.90	16.4	13.34	58.25	1,330	
2/ 8/14	3,620	186.3	60.5	10.00	16.3	11.21		1,140	
2/ 9/14	3,310	181.6	62.3	8.34	16.2	13.17		1,180	
2/10/14	982	81.7	20.8	0	5.3	9.92	58.17	1,300	Green day
2/11/14	929	77.1	20.8	0	5.1	9.33	57.56	1,155	Green day
2/12/14	2,138	124.1	178.1	13.80	9.9	11.59	57.84	1,515	Oatmeal day
2/13/14	2,177	127.1	178.1	19.22	10.3	10.87	57.93	1,580	Oatmeal day
2/14/14	2,171	126.7	178.1	31.08	10.2	10.54	57.80	1,930	Oatmeal day
2/15/14	917	76.1	20.8	0	4.8	9.92		970	Green day
2/16/14	3,487	181.9	61.6	0	16.2	14.96	57.35	1,130	Green day
2/17/14	3,464	180.1	60.7	Trace	16.3	12.89	57.75	1,000	
2/18/14	3,421	175.9	60.1	13.20	16.1	14.74	58.88	1,650	
2/19/14	3,361	170.2	59.7	9.10	15.9	14.01	58.45	1,320	
2/20/14	3,469	181.1	59.7	13.70	16.1	16.08	58.24	1,600	

TABLE 5—FELIX K. CLINICAL DATA—(Continued)

Date	Total Calories	Fat, Gm	Carbo- Hydrate Gm In Food	Glucose Gm In Urine	N In Food Gm	N In Urine Gm	Body Weight Kg	Urine Volume cc	Remarks
2/21/14	2,747	171.2	70.5	5.5	15.6	11.10	58.8	1,510	
2/22/14	2,747	173.0	61.2	Traces	15.7	10.70		1,460	
2/23/14	2,720	176.7	60.4	Traces	16.0	11.74	59.62	1,760	
2/24/14	2,705	174.8	58.6	Traces	14.7	11.15	59.17	1,400	Bread every two hours
2/25/14	2,460	181	58.3	Traces	16.0	12.30		1,600	
2/26/14	2,920	176.6	50.6	0	4.8	6.60	58.60	1,110	
2/27/14	2,922	174.8	42.1	0	14.6	15.68		1,450	
2/28/14	2,254	181.8	19.4	0	15.9	12.78	59.00	1,700	
3/1/14	2,494	218.4	58.2	0	14.4	15.68		1,600	
3/2/14	2,941	177.6	9.6	0	15.6	15.60	59.16	2,100	
3/3/14	2,826	177.7	58.4	0	15.6	12.70	58.87	1,540	
3/4/14	2,875	177.6	47.2	0	15.8	12.72	59.51	1,400	
3/5/14	2,400	178.4	50.3	0	16.0	12.80	60.68	1,510	
3/6/14	2,486	179.6	65.0	0	16.5	12.10	60.07	1,410	
3/13/14	2,800	178.5	58.5	5.75	15.2	15.20	59.52	1,650	Oatmeal every two hours
3/14/14	2,438	78.4	20.8	0	5.0	10.87	59.87	1,400	Green day
3/15/14	2,927	77.1	20.8	0	4.8	5.77	59.22	870	Green day
3/16/14	2,007	112.0	178.0	24.32	9.1	10.81		1,580	Bread day
3/17/14	2,013	112.6	178.0	27.03	9.2	8.85	58.81	1,390	Bread day
3/18/14	2,057	110.0	178.0	37.38	9.6	8.81		1,786	Bread day
3/19/14	2,42	78.1	20.8	0	5.0	6.48	58.42	930	Green day
3/20/14	2,46	78.7	21.2	0	4.8	7.88		1,577	Green day
3/21/14	2,388	173.1	61.4	0	15.6	11.98		2,180	
3/22/14	2,359	173.4	58.3	15.86	14.9	10.31		1,250	
3/23/14	2,164	199.5	60.7	Trace	15.0	11.01		1,820	

The vegetables were increased until on July 30 he was taking 70.5 gm carbohydrate, without glycosuria. Protein and fat were then slowly added, and an adequate diet attained without difficulty. Patient is a gourmand, and in September he was allowed to bring back his old symptoms by excess of fat in the diet, as an object-lesson. Two days' fasting stopped this glycosuria and suitable diet was resumed. In the latter part of October the average daily diet was approximately 114 gm protein, 120 gm carbohydrate, and from 2,600 to 2,900 calories. Calorimeter experiments were performed on October 30 and 31 and November 5. Patient was discharged on Nov 9, 1915, weighing 61.2 kg. He has done his usual work since, with only an occasional temporary glycosuria after eating too much.

CASE 5—Felix K. (mild diabetes), clerk, 47 years old, born in Ireland. As a young man the patient had pneumonia, urethritis, and about four years ago an attack of malaria. He was a heavy drinker of beer and whisky up to five months ago. Lately he has taken but little alcohol. About one year ago he first noticed a loss of weight, with polyuria and weakness. Since then he has lost from 40 to 50 pounds. On admission to Bellevue, Oct 28, 1913, he

was so weak that he could hardly walk upstairs. He is an emaciated man of medium stature. The lungs are emphysematous. There is slight exophthalmos, but no enlargement of the thyroid gland. Wassermann reaction ++; hemoglobin 98 per cent, leukocytes 9,500, blood pressure systolic 110, diastolic 75. His urine contained 61 gm of glucose, 2.14 gm ammonia, and small amounts of betaoxybutyric acid. The patient was in the general ward and it was difficult to control his diet. He was discharged on November 25, and on January 13 was readmitted, this time to the metabolism ward. Weight January 16, 56.5 kg. On a restricted diet his carbohydrate tolerance improved and his weight and strength increased rapidly (see Table 5). He was discharged March 24, 1914, in excellent condition. Since then he has reported from time to time, feeling perfectly well and strong, but showing sugar in the urine when he departs from his diet.

CASE 6—John O'C (mild diabetes, morphinism), clerk, aged 32. His father was an alcoholic. At the age of 15 the patient had typhoid, and he has suffered from "pleurisy" eight times in the past few years. At the age of 16 he began to smoke opium, later taking to hypodermic injections of the drug, and one year ago he added cocaine in increasing doses. Before admission he was taking 80 grains of cocaine and 22 of morphin a day. This is his first attempt at breaking the habit. About two years ago he noticed polyuria and polydipsia and his doctor found sugar in the urine. He did not follow treatment and lost weight rapidly. He was very constipated, and so weak that he could hardly walk. Admitted to Bellevue Hospital March 13, weight March 24, 31.3 kg, height 163 cm. He was found to be nothing but skin and bones, toothless, with bent figure and ratlike, pathetic face. His whole body was covered with abscesses and scars of infections from hypodermic injections. There was a small ulcer on the sole of each foot. His pulse was very small, the beat normal, his tongue fissured, glassy and moderately red.

On a restricted diet the patient improved slowly and the glycosuria and acidosis cleared up (Table 6). He grew stronger but it was almost impossible to increase his weight without causing glycosuria. It was necessary to give him a grain of morphin every four hours. His systolic blood pressure varied between 104 and 125. On May 1, 1915, he was discharged and sent to a sanitarium, where he stayed a short time, then went back to his old habits and died a few months later.

#### SUMMARY AND COMMENT

1 *The Oatmeal Treatment*—The mildly diabetic patient, Felix K., on a regulated diet containing about 60 gm carbohydrate daily, showed a constantly positive carbohydrate balance and maintained his weight and well-being. February 10 and 11 were "green" days. Then from February 12 to 14, inclusive, 200 gm oatmeal were given daily in the usual manner, then followed, February 15 to 16, two more "green" days. For comparison, beginning March 14, the same program was instituted, using bread instead of oatmeal, namely, first two "green" days, then March 16 to 18, inclusive, 265 gm bread daily, equivalent in carbohydrate to the previous oatmeal, with fat, protein and calories also corresponding to the oatmeal period, then March 19 and 20 two more "green" days. Comparison was also made in a different manner, as follows. On February 24 he was given 18 gm bread and 9 gm butter every two hours, and on March 13 was given the equivalent carbohydrate in the form of 13.6 gm oatmeal with 9 gm butter every two hours.



TABLE 6—JOHN O'C

Date	Food					
	Total Calories	Protein, Gm	Fat, Gm	Carbo- Gm	Alcohol Gm	Food, N Gm
March 24 25	2,527	66.1	144.2	51.7		10.57
March 25 26	1,842	51.1	141.2	70.4		12.47
March 26 27	2,605	64.9	160.1	77.6		11.04
March 27 28	2,601	74.4	147.7	84.2		12.70
March 28 29	2,410	54.1	155.9	84.6		15.13
March 29 30	2,505	52.1	195.9	85.2		15.13
March 30 31	2,410	196.6	185.6	87.5	11.47	17.05
March 31 April 1	2,370	57.5	164.5	70.6	22.94	14.69
April 1 2	2,488	58.7	183.7	62.4	22.94	14.19
April 2 3	1,709	60.6	147.5	43.2	22.94	11.13
April 3 4	294	0	0	0	42.00	0
April 4 5	1,575	25.7	60.6	16.6	45.90	5.71
April 5 6	1,941	44.1	126.5	142.5		7.05
April 6 7	1,504	47.0	87.8	142.5		7.52
April 7 8	1,742	47.0	104.8	142.5		7.52
April 8 9	2,145	57.2	194.3	25.9		9.15
April 9 10	1,459	79.8	152.0	23.9		6.36
April 10 11	1,783	48.1	151.4	36.6		7.70
April 11 12	2,282	71.3	193.2	47.1		11.41
April 12 13	2,435	76.0	200.7	61.6		12.16
April 13 14	2,921	77.9	199.2	36.5		12.46
April 14 15	2,178	70.6	187.6	37.0		11.29
April 15 16	1,723	28.9	147.6	28.5	89.10	4.62
April 16 17	1,781	43.7	144.8	23.8	22.94	4.62
April 17 18	1,600	34.4	114.4	25.3	42.00	5.50
April 18 19	1,748	31.0	128.5	25.5	45.90	4.96
April 19 20	1,579	41.4	110.2	41.5	30.59	8.62
April 20 21	1,919	49.6	152.8	32.8	22.94	7.93
April 21 22	1,874	49.2	148.0	28.2	22.94	7.87
April 22 23	1,952	77.3	140.3	41.4	22.94	12.37
April 23 24	2,063	100.9	142.2	40.8	22.94	16.14
April 24 25	1,679	67.6	115.2	41.8	22.94	10.82
April 25 26	385	16.8	34.0			2.69
April 26 27	1,761	99.0	133.0	28.9		15.84
April 27 28	737	25.3	60.6	16.7		4.05
April 28 29	1,652	47.5	93.4	143.6		7.60
April 29 30	1,674	47.0	96.3	142.5		7.52
April 30 May 1	1,652	47.5	93.4	143.6		7.60

CLINICAL DATA

Urine							Body Weight kg
Urine N, Gm	Excreta N, Gm ‡	N Balance, Gm	Urine Glucose, Gm	Urine NH <sub>4</sub> , Gm	Diacetic Acid	Urine Volume, c c	
13 34	14 40	-3 02	78 1			1,395	31 25
12 72	14 02	-1 05	55 7	1 70	Small amount	1,130	31 91
							32 16
{ 9 53*							
{ 9 93†	11 20	+1 50	39 4			900	32 61
10 09	11 40	+1 73	43 7			1 480	33 80
9 92	11 23	+1 90	70 9	2 04	++	2,310	33 88
9 25	10 05	+6 11	53 3	1 80	+	2,000	33 63
10 54	11 04	+2 06	40 6	2 18	+++	1,550	33 14
9 53	10 05	+3 24	33 4	1 96	++	1,125	32 89
9 25	10 36	+0 97	23 6	1 96	+	920	32 89
6 02			+++	0 67	0	500	32 11
6 81	7 38	-1 67	0	0 26	0	735	32 69
8 41	9 12	-2 00	20 7	0 41	0	1,280	
6 44	7 19	+0 33	40 6	0 41		3,875	34 81
4 51	5 35	+2 17	29 7	0 75	0	2,900	32 71
5 76	6 68	+2 47	Heavy trace	0 57	0	1,490	32 26
6 72	7 36	-1 00	0	0 61	0	2,670	32 52
7 31	8 09	-0 39	0	0 39		1,620	31 79
6 22	7 36	+4 05	0	0 49	0	1,400	
8 28	9 50	+2 66	11 8	0 96	0	2,570	32 38
6 73	7 98	+4 48	7 2	0 82	Slight trace	1,440	31 79
8 99	10 12	+1 17	11 4	1 12	+	2,240	32 46
5 55	6 01	-1 39	2 6	0 79	Trace	1,200	32 52
5 04	5 74	+1 25	Slight trace	0 76	Heavy trace	1,880	32 12
5 04	5 59	-0 09				2,500	
5 37	5 87	-0 91				1,925	32 05
6 22	7 08	+1 54	0		0	1,820	31 61
5 80	6 59	+1 34				1,840	32 35
5 39	6 18	+1 69	0	0 51	0	1,940	32 52
6 35	7 59	+4 78	0	0 47	0	2,000	32 25
9 83	11 44	+4 70	0	0 59	0	1,725	32 45
9 18	10 26	+0 56	4 8		0	825	32 44
6 37	6 64	-3 95	0		Very heavy trace	600	
11 43	13 01	+2 79	0	0 93	Heavy trace	960	31 04,
9 30	9 71	-5 66	0	0 93	Slight trace	660	31 88
8 58	9 34	-1 74	15 9	1 04	Trace	1,105	31 43
- 6 48	7 23	+0 29	21 2	1 14	0	1,960	32 46
6 39	7 15	+0 45	23 1	1 17	0	1,825	32 45

\* 23 hours      † 24 hours      § Urine N + 10 per cent of Food N

TABLE 7—DATA OF—

Subject, Date, Weight, Surface Area Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Gerald S 11/9/14 42.15 Kg 1.44 Sq M	Prelim	11 15							
	1	12 15	16.64	16.17	0.717	20.22	0.261	52.10	43.97
	2	1 15	16.32	16.1	0.724	20.55	0.261	52.94	47.51
	3	2 15	16.24	16.8	0.717	20.66	0.261	53.55	51.11
Gerald S 11/12/14 40.15 Kg 1.41 Sq M	Prelim	11 15							
	1	12 15	16.27	15.87	0.740	22.44	0.207	52.15	49.24
	2	1 15	16.55	17.45	0.709	23.51	0.207	51.71	54.44
	3	2 15	15.50	17.61	0.640	24.52	0.207	57.19	56.77
Gerald S 11/14/14 38.97 Kg 1.40 Sq M	Prelim	10 24							
	1	11 24	15.41	16.65	0.700	17.66	0.441	51.87	45.12
	2	12 24	15.55	15.54	0.705	18.65	0.441	51.45	49.85
	3	1 24	15.70	15.87	0.701	18.71	0.441	51.45	51.61
Gerald S 11/16/14 38.77 Kg 1.40 Sq M	Prelim	11 22							
	1	12 22	13.85	14.29	0.705	20.82	0.347	46.94	43.67
	2	1 22	14.59	14.84	0.715	26.65	0.347	48.18	49.69
	3	2 22	15.27	14.73	0.734	24.96	0.347	48.25	50.03
Gerald S 11/18/14 38.74 Kg 1.40 Sq M	Prelim	11 06							
	1	12 06	12.17	12.41	0.719	13.42	0.247	40.40	34.51
	2	1 06	13.09	13.45	0.718	13.97	0.247	42.82	38.89
	3	2 06	14.19	13.43	0.709	14.61	0.247	44.27	41.69
Gerald S 11/20/14 38.74 Kg 1.40 Sq M	Prelim	11 06							
	1	12 06	13.37	12.59	0.778	17.60	0.22	41.60	39.42
	2	1 06	12.20	12.82	0.692	16.68	0.22	42.06	41.23
	3	2 06	12.28	12.13	0.736	16.19	0.22	39.92	41.02
Gerald S 11/23/14 42.84 Kg 1.45 Sq M	Prelim	11 15							
	1	12 15	13.02	13.54	0.699	12.09	0.232	44.14	38.70
	2	1 15	13.64	12.61	0.786	13.10	0.232	41.76	38.23
	3	2 15	12.56	13.11	0.697	14.15	0.232	42.72	42.79
Gerald S 11/24/14 44.00 Kg 1.46 Sq M	Prelim	11 06							
	1	12 06	12.80	11.70	0.796	13.09	0.237	38.79	36.04
	2	1 06	13.56	13.91	0.707	13.95	0.237	45.44	39.79
	3	2 06	13.22	12.51	0.768	13.69	0.237	41.23	38.55
	4	3 06	12.10	11.85	0.742	14.13	0.237	38.78	38.96

§ Calculations in summary based on total O<sub>2</sub> and CO<sub>2</sub> for 3 hours

—CALORIMETER EXPERIMENTS

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp, °C	Average Pulse	Work-Adder, Cm	Non-protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohydrate	Per Kg	Per Sq M Meeh	
	36 28									Basal, D N assumed to be 1 53 on basis of R Q Very quiet
55 18	36 61	71	4	0 704	22 4	77 6	0	1 24	35 01	
55 57	36 85	76	8	0 714	22 1	77 9	0	1 26	35 51	
51 13	36 86	77	4	0 705	21 8	78 2	0	1 27	35 92	
	37 14									Second day of fast, basal Asleep 50 min
52 23	37 24	99	7 2	0 755	8 0	75 1	16 9	1 30	36 11	
54 77	37 26	102	10 5	0 711	7 4	91 3	1 3	1 41	39 27	Asleep 40 min
55 45	37 23	99	2 0	0 639*	7 3	92 7	0	1 42	39 61	Asleep 30 min
	36 54									Fourth day of fast, basal Asleep
49 33	36 68	81	7 8	0 68*	19 4	80 6	0	1 33	36 66	
41 13	36 42		7 6	0 69*	19 6	80 4	0	1 32	36 29	Asleep
51 95	36 44	79	12 0	0 68*	19 5	80 5	0	1 32	36 36	Asleep 45 min
	36 16								...	Basal
40 14	36 03		9 0—	0 695	15 5	84 5	0	1 20	32 86	Asleep
53 54	36 16		13 0—	0 703	14 8	84 0	1 2	1 24	34 17	Asleep
48 88	36 08	70	15 8—	0 754	14 8	72 4	12 8	1 25	34 22	Drank 20 c c whisky at 1 27 p m
49 10	36 08		17 0—	0 665	14 2	85 8	0	1 30	35 85	Asleep
	35 76									Basal
26 05	35 51		4	0 697	15 5	84 5	0	1 04	28 65	Asleep
39 33	35 52		4	0 705	14 6	85 4	0	1 11	30 37	Basal, asleep
53 62	35 84		12	0 764	14 1	70 1	15 8	1 14	31 40	Drank 20 c c whisky at 1 08 p m Asleep 40 min Asleep 55 min
53 62	36 14		13	0 676	13 2	86 8	0	1 22	33 38	
34 91	35 97		7	0 740	14 6	75 5	9 9	1 11	30 39	Asleep 55 min
	35 88									Whisky, 20 c c at 11 03 a m
37 70	35 78		6	0 773	14 7	66 7	18 6	1 07	29 50	Dozed
40 06	35 75		4	0 673	14 5	85 5	0	1 09	29 83	Dozed
42 74	35 81		3	0 724	15 3	79 2	5 5	1 03	28 31	Dozed
46 44	35 92		19	0 782	12 8	65 2	22 0	1 23	33 04	Restless
	35 99									Basal
37 09	35 95	47	8	0 681	13 9	86 1	0	1 03	29 29	Asleep 30 min
43 05	36 04		11	0 783	14 7	63 8	21 5	1 00	27 71	Awake
34 37	35 81	52	14	0 678	14 4	85 6	0	1 00	28 35	Awake
	35 85									Basal
36 30	35 85	52	4 0	0 794	16 2	59 9	23 9	0 90	25 29	Quiet
41 16	35 90	51	5 5	0 691	13 8	86 2	0	1 03	29 62	Quiet
40 63	35 96		5 0	0 762	15 2	69 2	15 6	0 94	26 88	Drank 1 drop of water
31 21	35 75	50	2 2	0 730	16 2	76 9	6 9	0 90	25 28	Quiet

\* R Q assumed as 0 707 for calculations

TABLE 7—DATA OF CALORIMETER—

Subject, Date, Weight, Surface Area, Linear Formula	Period	End of Period	Carbon Dioxide, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calorimetry, Cal	Heat Estimated, Cal
Gerald S 11/2/14 44.01 Kg 1.46 Sq M	Prelim	11 15							
	1	12 15	12.72	12.20	0.782	14.98	0.255	49.2	55.55
	2	1 15	11.21	12.49	0.775	15.14	0.255	46.96	57.95
	3	2 15	11.03	12.29	0.771	15.61	0.275	49.79	53.83
	4	3 15	11.87	12.08	0.780	15.97	0.275	41.51	49.58
Gerald S 11/2/14 44.27 Kg 1.47 Sq M	Prelim	11 27							
	1	12 27	11.78	11.69	0.742	21.28	0.225	46.18	50.28
	2	1 27	11.07	15.15	0.769	20.78	0.228	44.27	42.66
	3	2 27	14.89	14.15	0.762	20.24	0.225	46.63	41.57
	4	3 27	11.56	14.27	0.752	20.30	0.225	46.67	45.91
Gerald S 12/2/14 41.76 Kg 1.47 Sq M	Prelim	11 12							
	1	12 12	15.59	15.21	0.745	21.90	0.208	59.03	42.79
	2	1 12	13.27	12.57	0.768	22.51	0.208	41.48	42.54
	3	2 12	16.42	16.38	0.751	24.10	0.208	54.02	50.44
	4	3 12	14.97	17.09	0.779	23.89	0.208	46.31	44.84
Gerald S 12/1/14 45.91 Kg 1.46 Sq M	Prelim	11 09							
	1	12 09	15.81	14.79	0.778	19.79	0.204	48.09	41.88
	2	1 09	16.41			19.61	0.204	50.91*	44.13
	3	2 09	13.03	13.34	0.759	18.19	0.204	43.95	42.59
	4	3 09	14.85	14.53	0.743	18.78	0.204	47.68	45.93
Gerald S 12/7/14 42.58 Kg 1.45 Sq M	Prelim	11 10							
	1	12 10	14.77	13.78	0.780	18.90	0.216	45.69	40.83
	2	1 10	15.08	15.19	0.722	19.31	0.216	49.59	45.09
	3	2 10	13.93	13.15	0.770	18.21	0.216	43.48	44.85
	4	3 10	14.40	13.69	0.765	18.41	0.216	45.18	45.10
William G 1/11/15 43.28 Kg 1.53 Sq M	Prelim	11 20							
	1	12 20	13.39	12.62	0.772	16.14	0.170	41.83	40.94
	2	1 20	14.30	13.84	0.750	16.38	0.170	45.67	43.05
	3	2 20	13.74	14.26	0.701	16.45	0.170	46.60	47.13
William G 1/15/15 43.84 Kg 1.54 Sq M	Prelim	11 07							
	1	12 07	15.11	14.72	0.747	24.83	0.291	48.34	42.16
	2	1 07	14.49	15.73	0.670	24.11	0.291	51.03	47.43
	3	2 07	14.21	14.66	0.705	24.30	0.291	47.56	49.04
William G 1/22/15 37.87 Kg 1.46 Sq M	Prelim	11 12							
	1	12 12	15.29	16.38	0.679	17.02	0.382	53.05	49.18
	2	1 12	14.80	15.66	0.688	17.32	0.382	50.69	48.96
	3	2 12	15.46	15.87	0.708	18.36	0.382	51.42	51.88

\* Calc., from CO<sub>2</sub>, R Q assumed 0.778

—EXPERIMENTS—(Continued)

Direct Calorimetry (Rectal Temp), Cal	Rectal Temp, C	Average Pulse	Work Added, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per kg	Per Sq M Mech	
	36 12									Basal
33 16	36 03	48	3 5	0 743	15 4	74 8	9 8	0 97	26 27	Dozed
37 01	36 01		2 7	0 769	15 2	66 3	18 5	0 93	26 68	Dozed
37 25	35 95		0 5	0 765	15 4	66 2	18 4	0 92	26 44	At 1 17 drank 20 cc whisky from tube
33 07	35 75	51	2 8	0 659	15 1	84 9	0	0 94	26 91	Dozed
	36 31									Basal
37 96	36 28	53	4 7	0 732	13 1	79 8	7 1	0 86	24 61	Quiet
46 86	36 40	53	8 5	0 753	13 7	73 4	12 9	1 00	28 73	Quiet
40 21	36 32	56	16 5	0 755	13 0	71 0	16 0	1 05	30 26	Drank 170 cc water at 1 28 p m
44 22	36 28	52	9 4	0 720	13 0	82 8	4 2	1 05	30 29	Quiet
	36 66									Basal
39 51	36 53	56	5 1	0 733	11 1	78 6	10 3	1 12	32 24	Quiet
37 03	36 44	55	1 1	0 762	13 3	70 8	15 9	0 93	26 73	Quiet
52 36	36 50	58	15 4	0 745	10 2	76 3	13 5	1 21	34 81	Exercised 10 min
49 81	36 64	53	5 8	0 774	11 9	63 9	19 2	1 04	29 84	Quiet
	36 08									
48 84	36 29	53	2 6	0 773	11 0	69 6	19 4	1 12	31 96	Exercised 10 min
51 94	36 51		5 7	.						Exercised 10 min
43 85	36 55	59	2 9	0 752	12 3	74 6	13 2	1 00	28 67	Quiet
43 22	36 48		2 8	0 734	11 3	81 4	7 3	1 09	31 11	Quiet
	36 46									Basal
43 09	36 53	55	21 2	0 776	12 5	65 4	22 0	1 07	30 42	Quiet
48 78	36 64	56	19 4	0 711	11 6	87 2	1 2	1 17	33 02	Quiet
43 58	36 61	54	25 4	0 765	13 2	67 9	18 9	1 02	28 95	Quiet
44 95	36 61	56	23 6	0 759	12 7	71 3	16 1	1 06	30 08	Quiet
	36 76									Basal
42 16	36 80	65?	2 9	0 767	10 8	69 7	19 5	0 97	27 57	Asleep
38 53	36 68	65?	10 7	0 743	9 8	79 7	10 5	1 10	30 10	Awake, quiet
48 46	36 72	53	7 4	0 689§	9 7	90 3	0	1 10	30 72	Awake, quiet
	36 75									Basal, D N 3 81 †
37 58	36 63	64	7 0	0 757	7 9	75 2	16 9	1 10	31 57	Asleep
47 22	36 63	64	9 6	0 673	7 4	92 6	0	1 16	33 33	Asleep
52 84	36 74	62	9 6	0 712	8 0	90 7	1 3	1 10	31 06	Asleep
	36 98									Basal, D N 3 12
46 13	36 89	64	8 5	0 679	10 8	89 2	0	1 40	38 19	Dozed
46 55	36 82	64	2 2	0 689	11 3	88 7	0	1 34	36 50	Quiet
52 30	36 84	63	6 5	0 713	11 1	88 9	0	1 40	37 02	Quiet

† D N assumed as 3 65 for calculations  
§ R Q assumed as 0 707 for calculations

TABLE 7—DATA OF CALORIMETER—

Subject, Date, Weight, Surface Area Linear Formula	Period	End of Period	Carbon Dioxide, Gm	Oxygen, Gm	R Q	Water, Gm	Urine & per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Limi- nated, Cal
Joseph L 2/1/17 49.14 kg 1.45 Sq. M.	Prelim	11 15							
	1	12 15	11 56	11 45	0.754	18 41	0.188	37 45	42 09
	2	1 15	11 57	11 56	0.747	17 79	0.188	36 99	42 18
	3	2 15	11 59	11 67	0.745	16 90	0.188	36 35	40 80
Edward M 10 30/14 66.70 kg	Prelim	11 15							
	1	12 15	20 58	18 19	0.853	2 35	0.791	60 77	62 97
	2	1 15	20 58	19 23	0.787	26 61	0.591	63.80	66 35
Edward M 10 31/14 66.72 kg	Prelim	11 53							
	1	12 23	21 62	19 58	0.791	25 92		66 23	54 37
	2	1 23	21 61	20 01	0.765	23 56		66 29	61 79
	3	2 23	22 61	20 27	0.812	24 57		67.59	66 77
Edward M 11/5/14 62.16 kg	Prelim	11 17							
	1	12 17	24 03	21 08	0.756	25 64	0.591	78 49	67 80
	2	1 17	23 27	21 55	0.745	28 66	0.791	80 21	76 64
	3	2 17	24 33	23 40	0.756	28 88	0.591	76 57	79 61
Felix K 2/11/14 57.36 kg	Prelim	11 15							
	1	12 15	20 18	19 36	0.758	22 51	0.325	63 71	66 09
	2*	2 15	44 10	45 06	0.745	44 78	0.650	141 40	140 20
Felix K 2/12/14 57.84 kg	Prelim	12 05							
	1	1 05	25 25	24 14	0.761	25 89	0.607	79 14	71 51
	2	2 05	26 63	24 85	0.779	31 64	0.607	81 91	80 43
	3	3 05	24 91	23 91	0.757	41 94	0.607	78 40	96 59
Felix K 2/14/14 57.80 kg	Prelim	11 08							
	1	12 08	25 79	23 83	0.787	23 97	0.481	78 91	75 60
	2	1 08	21 78	21 55	0.836	26 91	0.481	72 18	78 93
	3	2 08	21 53	21 55	0.828	27 69	0.481	72 03	80 44
Felix K 2/24/14 58.70 kg	Prelim	12 20							
	1	1 20	22 67	21 44	0.769	18 70	0.362	70 96	78 23
	2	2 20	22 61	20 08	0.810	19 99	0.362	67 18	77 64
	3	3 20	22 89	21 19	0.786	20 82	0.362	70 27	76 74
Felix K 2/26/14 58.57 kg	Prelim	11 02							
	1	12 02	21 00			18 95	0.326		75 40
	2	1 02	21 76	20 52	0.771	20 88	0.326	67 66	76 05
	3	2 02	21 64	19 60	0.808	20 55	0.326	65 30	74 30
Felix K 3/13/14 59.29 kg	Prelim	11 50							
	1	12 50	21 60	20 44	0.768	21 60	0.789	66 62	74 07
	2	1 50	21 63	20 31	0.774	20 94	0.789	66 29	72 80
	3	2 50	22 03	20 03	0.800	21 42	0.789	65 80	73 09

—EXPERIMENTS—(Continued)

Direct Calorimetry (Rectal Temp.), Cal	Rectal Temp., C	Average Pulse	Work-Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Protein	Fat	Carbohyd	Per kg	Per Sq M Meeh	
	36 56									Basal
36 33	36 39	72	3 0	0 723	13 3	82 6	4 1	0 93	25 95	Very quiet
40 52	36 35	72	2 5	0 733	13 5	76 5	10 0	0 92	25 63	Very quiet
30 62	36 05	73	12 0	0 739	13 7	76 3	10 0	0 91	25 20	Quiet
	37 31									Basal
55 09	37 16	52	34	0 827	17 1	48 0	35 0	1 00	32 74	Restless
55 99	36 96	53	21	0 784	16 3	70 2	21 1	1 05	34 37	Quiet
	36 76									97 gm olive oil at 10 03 a m
58 10	36 84	64	27					1 09	34 74	Quiet
65 49	36 92	60	20					1 09	34 78	Quiet
66 45	36 92	55	46					1 11	35 62	Restless
		.						1 10	35 00	Urine lost
	36 94	.								Breakfast at 7
69 54	36 98	71		0 743	20 0	70 7	9 3	1 26	40 63	96 gm olive oil at 9 17 a m
78 39	37 02	60		0 734	19 6	73 8	6 6	1 29	41 52	Quiet
78 80	37 01	67		0 743	20 6	70 2	9 2	1 23	39 63	Quiet
	37 18									Basal
49 49	36 84		5 6	0 751	14	73	13	1 11	34 74	Asleep
148 21	37 06	69	38 5	0 736	12	79	9	1 23	38 53	Fairly quiet
	37 53							.		At 10 45 to 10 52
64 43	37 39	80	6 8	0 749	20	68	12	1 37	42 99	oatmeal, 125, butter, 15, protein, 18 8, fat, 19 8, carb, 89 1
89 21	37 42	79	24 4	0 773	20	62	18	1 42	44 49	
88 69	37 28	71	26 0	0 744	21	69	10	1 35	42 59	
	37 21									At 9 45 to 9 53
70 91	37 12	76	12 5	0 783	16	62	22	1 37	42 89	oatmeal, 125, butter, 15
78 10	37 11		21 9	0 843	18	44	38	1 25	39 23	
80 50	37 17	85	13 0	0 833	18	47	35	1 25	39 15	
	37 19									Bread, 18, butter, 9, every 2 hrs, last taken at 11 37 a m
71 53	37 06		7 5	0 774	14	66	20	1 21	38 15	
74 35	37 00	69	8 3	0 822	14	52	34	1 14	36 09	
77 84	37 03	75	7 4	0 783	14	63	23	1 19	37 78	
	37 08									Basal
72 11	37 02	72	6 8							Very quiet
73 10	37 06		7 9	0 769	13	68	19	1 15	36 44	Very quiet
74 45	37 07	75	10 0	0 802	13	59	28	1 12	35 16	Very quiet
	36 87									Oatmeal 13 6, butter 9, every 2 hrs, last taken at 11 07 a m, asleep 1st period and half of second
65 35	36 70	76	9 0	0 751	31	58	11	1 12	35 59	
72 95	36 71	76	7 2	0 760	32	55	13	1 12	35 41	
74 71	36 75	75	13 2	0 798	32	47	21	1 11	35 15	



TABLE 7—DATA OF CALORIMETER—

Subject Date, Weight, Surface Area Linear Formula	Period	End of Period	Carbon Dioxid, Gm	Oxygen, Gm	R Q	Water, Gm	Urine N per Hour, Gm	Indirect Calo- rimetry, Cal	Heat Elimi- nated, Cal
Edly K 3/18/14 58.2 Kg	Prelim	11 15							
	1	12 25	23.53	22.18	0.781	22.75	0.373	73.47	71.51
	2	1 25	24.41	21.60	0.812	25.72	0.373	73.12	70.87
	3	2 25	22.15	19.18	0.810	21.78	0.373	64.42	73.67
	4	3 25	22.67	19.51	0.810	21.28	0.373	66.01	74.31
Edly K 3/20/14 57.51 Kg	Prelim	1. 00							
	1	1 00	18.79	17.51	0.779	18.15	0.328	57.97	60.50
	2	2 00	20.17	19.00	0.748	19.60	0.328	64.21	65.02
	3	3 00	20.25	18.92	0.778	20.01	0.328	62.58	61.95
John O'C 4/28/15 71.15 Kg 1.20 Sq M	Prelim	11 51							
	1	12 21	14.96	9.92	0.732	24.31	0.281	16.05	47.99
	2	1 31	15.07	9.45	0.812	24.86	0.281	44.74	48.82
John O'C 4/30/15 72.45 Kg 1.22 Sq M	Prelim	11 46							
	1	12 46	14.25	12.85	0.891	22.66	0.262	42.80	43.58
	2	1 46	14.57	14.11	0.715	26.25	0.262	46.63	50.53

**Glycosuria** The urine always became promptly and completely sugar-free on "green" days. The total amount of glucose excreted during the oat period was 64.1 gm, during the bread period 88.8 gm. This difference is fully comparable to those in the literature upon which the claims of superiority of oatmeal have been based. But, as Blum pointed out, spontaneous fluctuations in diabetic glycosuria must be allowed for, even when all conditions are kept as uniform as possible, and a repetition of the same test sometimes gives a variation in the opposite direction. The more favorable carbohydrate balance in this instance speaks no more for oatmeal than the less favorable nitrogen balance during this same time speaks against oatmeal. This interpretation is supported by the results of the other test, for on the days when the carbohydrates were given in small divided doses it so happened that the glycosuria from bread was only a trace, while that from oatmeal amounted to 5.75 gm. A consistent difference in favor of oatmeal is therefore not present.

**Respiration Experiments** This patient on February 12, while fasting in the morning after a "green" day of eggs, butter and green vegetables of the 5 per cent class, derived from 10 to 13 per cent of the calories from carbohydrate. On the first oatmeal day he derived 13

## —EXPERIMENTS—(Continued)

Direct Calo rimetry (Rectal Temp), Cal	Rectal Temp, C	Aver age Pulse	Work- Adder, Cm	Non protein R Q	Per Cent Calories from			Calories per Hour		Remarks
					Pro tein	Fat	Carbo hyd	Per kg	Per Sq M Meeh	
	37 16									At 9 45 to 10 06 a m, bread 168, butter 15
63 34	36 99	67	11 3	0 777	13	66	21	1 12	39 67	
81 41	37 07	73	28 3	0 813	14	55	31	1 25	39 48	
69 51	37 01	71	22 2	0 847	15	44	41	1 10	34 78	
68 62	36 94	70	27 0	0 811	15	55	30	1 13	35 66	Basal Asleep 30 min Quiet Quiet
	36 88									
51 32	36 65	59	10 6	0 774	15	65	20	1 00	31 51	
66 74	36 80	60	15 1	0 739	14	76	10	1 11	34 97	
67 66	36 88	62	13 3	0 774	14	66	20	1 08	34 01	1st oatmeal day Oatmeal 50, butter 10, at 6 30 a m and again at 9 34 a m, restless 2d period 3d oatmeal day Same food as above Quiet
	36 43									
45 42	36 34	58?	16 1	0 711	21 9	77 0	1 1	1 47	37 56	
48 22	36 33	76?	22 8	0 814	22 6	50 0	27 4	1 42	36 49	
	36 32									Quiet Restless
42 28	36 27	67	9 0	0 807	16 2	54 1	29 7	1 32	34 19	
46 71	36 15	72	18 0	0 757	14 9	69 4	15 7	1 44	37 25	

per cent, and on the third oatmeal day 32 per cent from carbohydrate. If the metabolism of carbohydrate continued at this rate of 32 per cent throughout the day, he could have utilized about 145 gm. The positive carbohydrate balance on that day was 149 gm. On March 18, the third day on which he received the same amount of starch in the form of bread, he derived 31 per cent of his calories from this source, he utilized about 130 gm, and the positive balance was 147 gm. He was able to derive 26 per cent of his calories from carbohydrate after small divided meals of bread and butter, and as much as 24 per cent while fasting on the morning after his usual diet, which just kept him sugar-free. After similar doses of oatmeal he derived only 15 per cent from carbohydrate. The respiration experiments therefore show no significant difference between the starch of bread and that of oatmeal in this case.

The morphin addict, John O'C, with mild diabetes, gave exactly the same results, namely, on the first oatmeal day, April 28, 14 per cent from carbohydrate, on the third day, April 30, 23 per cent. He was not tested with bread.

It is quite possible that the slightly lower combustion of carbohydrate indicated by the quotients on the first as compared with the

TABLE 8—INDIRECT

Subject and Date	Character of Experiment	Calories per hr	Average Calories per Hour		Per Sq. M., Linear
			Per Sq. M., Mech.	Per Cent from Average Normal, 247	
Gerald S.					
11/9/14	Basal	126	35.6	+2	26.7
11/12/14	Basal, second day of fast	128	35.3	+11	29.18
11/14/14	Basal, fourth day of fast	132	35.4	+5	26.4
11/16/14	Basal, sixth day of fast	122	33.5	-3	33.9
	Two hours after whisky	125	35.0	-2	35.4
11/18/14	Basal, eighth day of fast	108	29.5	-15	29.8
	Three hours after whisky	115	31.7		32.0
11/20/14	Four hours after whisky	111	30.2		30.7
11/22/14	Basal, fifth day of feeding	109	28.5	-18	29.6
11/24/14	Basal, sixth day of feeding	095	26.8	-23	28.0
11/25/14	Basal, seventh day of feeding	092	26.5	-24	27.7
	Two hours after whisky	093	26.7		28.0
11/30/14	Basal (with water drinking)	099	28.5	-18	31.4
12/2/14	Basal	102	29.5	-15	31.0
	Basal with exercise	112	32.3		34.8
12/4/14	Exercise with basal	107	30.6		32.7
12/7/14	Basal	108	30.6	-12	31.8
William G.					
1/11/15	Basal	103	29.5	-15	29.3
1/15/15	Basal	112	32.0	-8	31.9
1/22/15	Basal	137	37.2	+7	35.5
Joseph L.					
2/1/15	Basal	092	25.6	-26	25.4
Edward M.					
10/30/14	Basal	103	33.6	-3	
10/31/14	Two to five hours after 97 gm olive oil	110	35.0		
11/5/14	Two to five hours after 96 gm olive oil following breakfast	129	40.9	+17	
Felix K.					
2/11/14	Basal after 1 green day	119	37.3	+7	
2/12/14	1½ to 4¼ hours after 125 gm oatmeal, 15 butter	138	43.4		
2/14/14	1½ to 4¼ hours after 125 gm oatmeal, 15 butter, third oatmeal day	129	40.4		
2/24/14	After 18 gm bread and 9 butter every two hours	118	37.3		
2/26/14	Basal	118	35.8	+3	
3/13/14	After 13.6 oatmeal and 9 butter every two hours	112	35.4		
3/18/14	1½ to 5½ hrs after 168 bread and 15 butter, 3d bread day	118	37.4		
3/20/14	Basal after one green day	106	33.5	-4	
John O'C.					
4/28/15	After 100 gm oatmeal and 20 butter, first oatmeal day	145	37.0	(+7)	37.7
4/30/15	After same food, third oatmeal day	138	36.7	(+3)	36.7

\* On account of respiratory quotient, dextrose nitrogen ratio assumed to be 1.53 for purpose of calculation  
† Nonprotein respiratory quotient assumed 0.707 for calculations

# CALORIMETRY SUMMARY

Per Cent from Average Normal 39.7	Average R Q	Average Non protein R Q	Per Cent Cal from Carb	Per Cent Divergence of Direct from Indirect Cal	Average Pulse	Remarks
- 8	0.719	0.707*	0	+ 2	75	Very quiet, D N 1.53 <sup>2*</sup>
- 1	0.697	0.700§	0§	- 2§	100	Asleep, D N 3.5
- 8	0.702	0.68†	0	- 8	80	Asleep, D N 1.0
-15	0.710	0.701	1	- 1		Asleep, D N 1.55
	0.717	0.710	6	- 1	70	Asleep, D N 1.55
-25	0.716	0.701	0	-21		Asleep, D N 0.33
	0.737	0.727	6	+ 6	71	Awake, D N 0.33
	0.748	0.739	10	+ 1	61	Dozed
-26	0.727	0.712	2	-11	49	Awake
-29	0.753	0.744	10	- 9	51	Quiet
-30	0.764	0.756	14	-14	48	Dozed
	0.726	0.712	1	-14	51	Dozed
-21	0.749	0.740	10	- 7	55	Quiet
-22	0.757	0.750	13	-16	56	Quiet
	0.765	0.760	16	+ 2	56	Flexed arms 10 min
	0.760	0.753	13	- 2	59	Flexed arms 10 min in first two periods
-20	0.759	0.753	15	- 2	55	Quiet
-26	0.741	0.732	7	- 4	61	Quiet
-20	0.707	0.714	0	- 6	63	Very quiet, dozed, D N 3.8†
-11	0.692†	0.693	0	- 7	64	Quiet, D N 3.12
-36	0.743	0.733	8	- 3	72	Very quiet
	0.805	0.806	28	-11	53	Fairly quiet
	0.789			- 5	59	Fairly quiet, urine lost
	0.753	0.740	8	- 4	69	Quiet, breakfast at 7 a.m., Prot 44, fat 204, Carb 38
	0.749	0.741	10	- 4	69	Fairly quiet
	0.766	0.755	13	+ 1	77	Fairly quiet
	0.817	0.820	32	+ 3	81	Fairly quiet
	0.791	0.793	26	+ 7	72	Quiet
	0.787	0.786	24	+11	74	Very quiet
	0.781	0.770	15	+ 7	76	Asleep one half exper
	0.811	0.812	31	+ 2	70	Fairly quiet
	0.768	0.762	13	+ 0	60	Quiet
(- 5)	0.772	0.763	14	+ 3	64	Fairly quiet
(- 8)	0.784	0.782	23	- 1	69	Fairly quiet
				Av ± 5.5		

† D N ratio assumed to be 3.65 for calculations

§ Calculated from total O<sub>2</sub> and CO<sub>2</sub> for three hours

third day of carbohydrate diet may indicate storage of glycogen after impoverishment on the preceding vegetable day, in harmony with the observations of Johansson and others on this point. The experiments fail to confirm Falta's conception of a striking difference in the manner of utilization of carbohydrate by diabetics on the first and third days of such a "cure." It would be desirable also to have information concerning the behavior of a normal subject under the same conditions, but such an experiment was not included in the present series.

**Carbohydrate and water retention.** The quantities of carbohydrate not accounted for by combustion are in all these experiments such as may easily be assumed to be stored as glycogen. The experiments are not of a character such as to throw light on the fate of carbohydrate under circumstances when, as Joslin<sup>1</sup> reckons, as much as 520 gm may be retained and not accounted for by differences in the respiratory exchange. The fate of carbohydrate under these conditions must be regarded as not definitely settled. Glycogen storage is known to be commonly associated with water retention. Aside from the edema which authors have shown to be attributable to sodium chlorid and bicarbonate, the gain in weight of some diabetics during the oatmeal treatment may be related to the carbohydrate retention. It will be noted that the patient John O'C actually gained about a kilogram in weight during the oatmeal period. On the other hand, Felix K, with a larger carbohydrate intake and apparent storage, gained no weight during his oatmeal period and lost a trifle during the bread period. This result therefore stands in marked contrast to the well-marked increase in weight which ordinarily occurs when a normal person changes from carbohydrate-poor to carbohydrate-rich diet.

**2 The Dextrose-Nitrogen Ratio.**—The cases of interest in this connection are those of William G, Gerald S, and that of Cyril K, which was described by Geyelin and DuBois, also another case more recently observed, a description of which will be published shortly by Gephart, Aub and DuBois.

William G, as previously stated, at first upon admission to the Presbyterian and Rockefeller Hospitals was found to show a dextrose-nitrogen ratio of approximately 3, with a strongly negative nitrogen balance. Table 4 contains his record six months later, during a period of feeding in the attempt to improve his strength. Starting with sugar-free urine on January 11, increase of protein and fat in the diet produced prompt glycosuria, with dextrose-nitrogen ratios higher than before. At least on January 15 and 20 the ratio was that of "total" diabetes. The actual quantities of both sugar and nitrogen excreted were less than in the former period when the ratios were smaller, and the nitrogen deficit was less although the diet was lower than before in both protein and calories. The clinical condition changed so rapidly

for the worse and the patient on January 22 was so ill and drowsy that it was necessary to resort to fasting to avert coma

In Gerald S the dextrose-nitrogen ratio was confused by the presence of carbohydrate in the diet until November 11. On this day no food was taken except 50 c c cream at 6 a m. The ratio for the twenty-four hours November 11-12 was 3.68. The excessive nitrogen excretion which was a prominent feature with William G. was absent here. The fall in both glycosuria and ratio during fasting is evident from Table 2.

Cyril K., the patient of Geyelin and DuBois, fasted five days without abatement of any of the diabetic symptoms, and with acidosis steadily increasing either because of the fast or in spite of it. Then, on account of dyspnea and drowsiness threatening coma, he was given low diet for a few days, consisting chiefly of protein, though containing also 53.3 gm carbohydrate December 14 and 23.5 gm December 15. The dextrose-nitrogen ratios for the next three days (December 15 and 17 inclusive) were 3.97, 4.01, and 3.87. The nitrogen loss at this period was greater than ever before described in uncomplicated diabetes. Beginning December 17, the condition gradually yielded to the second fast-treatment, as indicated by the fall of sugar, nitrogen, the ratio and the acidosis.

The case of Gephart, Aub and DuBois appeared at first to be of no extreme severity, and the urine was readily cleared up by fasting. Thereafter, in consequence of excessive protein-fat diet and the simultaneous development of an alveolar abscess, glycosuria suddenly appeared, and by the second day the 3.65 ratio was attained. The condition then yielded promptly to a repetition of fasting.

It is desirable here to discuss the dextrose-nitrogen ratio as respects (a) its occurrence in human diabetes, (b) its practical and (c) its theoretical significance.

(a) Lusk has insisted that trustworthy ratios are obtainable only when the diet contains no appreciable quantity of carbohydrate. The examples in the entire literature are very few, largely because the type of patients most likely to show the maximum ratio has so seldom been subjected to the conditions necessary to establish the ratio. Foster<sup>28</sup> says "The diabetic patient is for several reasons an extremely difficult subject for these experiments. It is usually impossible to restrict him for a period of a week to a fat-protein diet." Benedict and Joslin<sup>4</sup> mention the danger of placing a patient with severe diabetes upon a strict protein-fat diet for several days. Joslin<sup>5</sup> also calls attention to possible errors due to excretion of retained carbohydrate unless ade-

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28 Foster, N. B. *Diabetes Mellitus*, Lippincott Co., Philadelphia and London, 1915, p. 30.

quate precautions are taken. The conditions involved in fasting differ in some respects from those of protein-fat diet. Though sometimes an existing ratio of 3.6 rapidly diminishes on fasting, and the glycosuria clears up, in other cases this ratio is clearly developed and persists for at least several days. Since the introduction of the fasting treatment, examples, mostly unpublished as yet, of such a ratio have been observed by several clinicians. It is probable that such observations will henceforth be made more frequently, not because the incidence of such "total" diabetes is increased by the fasting treatment, but because this method involves placing severely diabetic patients as a routine measure upon a program of complete carbohydrate abstinence for considerable periods, thus facilitating demonstration of the ratio with freedom from previous difficulties and errors. This is one of the features in which the new treatment has proved of service not merely for the practice but also for the theory of diabetes.

(b) Recent experience confirms the suggestion of Lusk<sup>19</sup> that the presence of the above-mentioned ratio need not be permanent or carry a rapidly fatal prognosis. In the patient as in the phlorhizinized animal the relation between sugar and nitrogen in the urine under suitable conditions is an index of the deficiency of carbohydrate combustion, and the maximal ratio shows total absence of utilization of the sugar formed from protein. This ratio does not necessarily indicate the highest possible quantity of protein catabolism or sugar excretion. The nitrogen excretion of Gerald S. was never high. William G. showed markedly excessive protein destruction at first, later (January 15) the ratio was maximal, but the protein breakdown moderate. Cyril K., as above remarked, showed the most rapid nitrogen loss ever recorded in a case of diabetes and this loss was still excessive on December 22-23, when the ratio had fallen to 1.12. Phlorhizin given to Gerald S. could not have increased the ratio but would perhaps have increased the quantities of sugar and nitrogen excreted.<sup>20</sup> The reason for the remarkable intensity of protein catabolism in some cases is not known. There is no justification for the term "toxic" applied by Magnus-Levy and others. So far as existing data permit judgment, the difference does not lie in acidosis, for the patients mentioned seemed about equally close to coma. The bodily strength and nutritive state may play a considerable part. For example, Cyril K. (Geyelin and DuBois), with recent acute diabetes, had the necessary strength and reserves for intense waste of sugar and nitrogen, like the typical experimental animal. Gerald S. was weak and emaciated. William G.

29 This remark applies to fasting. On liberal protein-fat diet Benedict and Lewis (The Influence of Induced Diabetes on Malignant Tumors, *Proc Soc Exper Biol and Med*, 1914, xi, 134), found the nitrogen excretion of human subjects not increased by "total" phlorhizination (personal communication).

was weaker in the second of the periods described than in the first, and weighed some 5 kg less. But this may not be the whole explanation. A specific disorder affecting protein metabolism in some patients, as in totally depancreatized dogs, is not excluded. The possibility of very rapid changes in the ratio, as exhibited most strikingly by the patient of Gephart, Aub and DuBois, is one of the strongest evidences in favor of the functional element in human diabetes. Such sudden changes for the worse or for the better are scarcely to be expected in the case of purely organic lesions, and are contrary to the results in animals when the islands of Langerhans have been lost. Because of the generally more favorable outlook for functional as opposed to organic disturbances, the dextrose-nitrogen ratio therefore contributes something to the prognosis in human diabetes. For the very reason that the process is at least partly functional and under appropriate treatment may be temporary the dextrose-nitrogen ratio fails to define the later prognosis in any individual case. Aside from the duration of the trouble and other fallible clinical indications, there is now no basis for predicting which patients are likely to recover tolerance quickly and in considerable degree, and which are likely to improve slowly and in slight measure. Experience to date indicates that cases of brief acute course, when checked by radical treatment, may show a correspondingly more rapid improvement as compared with the more protracted cases in patients of corresponding age and type. The occurrence of the dextrose-nitrogen ratio of the phlorhizinized dog in any human patient may be taken as a sign of the gravest immediate significance. The few known to have exhibited this ratio during fasting have died, except the patient of Geyelin and DuBois. The exception is believed to be due to the skilful alternation of fasting and protein feeding in this case, but further experience will be necessary for decision. It is at least established that careful treatment offers some hope even in cases of this type, and that with the worst of ratios and other symptoms an appreciable carbohydrate tolerance may subsequently be regained.

(c) The principal debate concerning the dextrose-nitrogen ratio has been not whether values as high as those mentioned occur in human patients, but whether any higher values ever occur. Animal experiments aiming to prove the formation of sugar from fat have all miscarried, but a few authors still hold that occasional cases of exceptionally severe human diabetes show dextrose-nitrogen ratios so high as to be explainable only by the formation of sugar from fat. Some of the cases above described are not lacking in severity, but rather give the impression of being more severe than those in the literature in which sugar was supposed to have been formed from fat, and neither on protein-fat diet nor on fasting were any ratios observed which could justify the assumption of sugar-formation from fat. It may be argued



that the negative evidence in the present cases cannot overthrow positive evidence in other cases, which though not more severe may have been of peculiar character. Alone, it could not do so. But the carbohydrate hunger of patients on old-fashioned protein-fat regimen caused numerous writers to compare them to drug addicts with respect to their ingenuity, pertinacity and also mendacity in obtaining forbidden food, even when supposedly isolated and watched, and experienced observers are aware that only special environment and special qualifications of the nurse in charge can guarantee against this source of error. As accuracy of investigation has increased, the number of reports of ratios indicating sugar formation from fat has diminished. Apparently no such ratio has ever been described in America, and the experience of the majority of clinics and laboratories elsewhere is similar. The justification for questioning the alleged findings in occasional cases at a few European clinics is found in the large number of accurate observers who see numerous diabetics of various grades of severity, but are still waiting to see any case showing the excessive ratios mentioned. The general agreement of negative evidence is believed now sufficient to set aside the principal support of the doctrine of sugar formation from fat, namely, the supposed occurrence of this process in diabetic patients.

3 *The Respiratory Quotient*—In the cases mentioned, except that of Cyril K, the Lusk dextrose-nitrogen ratio was present only for brief periods. The objection might therefore be raised that these ratios were purely accidental, and partly accounted for by sweeping out of more or less carbohydrate previously retained as glycogen or sugar. Here the necessary proof is afforded by the respiratory quotients. In the case of Gerald S. it was impossible to determine accurately the dextrose-nitrogen ratio November 9, the day after a considerable amount of carbohydrate in the food, so it was assumed for purposes of calculation to be 1.5, a figure which gave theoretical results. On the second day of the fast, the dextrose-nitrogen ratio being 3.5 during the calorimeter period, the total quotient was 0.697 and the nonprotein quotient 0.7. On the sixth and eighth days of the fast the nonprotein quotients were 0.701 and 0.701 respectively. For William G. in the last two experiments (January 15 and 22), with dextrose-nitrogen ratios of 3.81 and 3.12 during the calorimeter periods, nonprotein quotients of 0.714 and 0.693 were found. The average nonprotein quotient on all these days was 0.703, as compared with the theoretical figure of 0.707 for fat. These and the similar quotients observed in Cyril K. serve to show that the dextrose-nitrogen ratios obtained under the above conditions were not accidental, but at the times when the Lusk ratio was present the diabetes was actually "total." These quotients also agree with the results of Benedict and Joslin and other exact work in fur-

nishing additional testimony against the formation of sugar from fat, thus fully confirming the evidence afforded by the dextrose-nitrogen ratio

The tables also show that during the fasting treatment the power to oxidize carbohydrate gradually improved, as would be expected from the urinary findings. On fasting and on low diet thereafter the patients were able to derive an appreciable percentage of the energy requirement from this source. Joseph U. was able thus to derive 8 per cent of his requirement. Gerald S., from a condition of total inability to oxidize sugar, apparently became able to derive 15 per cent of his energy from it. William G. illustrated the opposite change produced by protein-fat overfeeding. January 11, on low diet, he was deriving 7 per cent of his requirement from carbohydrate. The protein and fat were then increased, and by January 15 "total" diabetes was present.

Brief mention may also be made of the two exercise experiments with Gerald S. on December 2 and 4. The exercise performed in the calorimeter consisted in flexing and extending the forearms for ten minutes at the beginning of a period. The labor performed was sufficient to raise the heat production by 18 per cent for the hour period, or by about 100 per cent for the ten minutes of actual exercise. The respiratory quotient showed no change during this hour, remaining at 0.75, but in the next hour the total quotient was 0.779 and the nonprotein quotient 0.77, which figures are higher than the averages obtained in any of the experiments with this patient at rest. On December 4 a similar ten minutes of exercise was inserted at the beginning of the preliminary period, immediately after the calorimeter was sealed, and also at the beginning of the first and second hours thereafter. The quotient in the first hour was 0.778, corresponding to that on December 2, the quotient in the second hour was lost through accident. The experiments at least give no indication of a lowering of the quotient due to any hypothetical exhaustion of glycogen in a patient supposedly glycogen poor. This aspect is to be emphasized more than the slight rise of the quotient, which might have been accidental in the two experiments, though it may perhaps suggest a slight increase in carbohydrate utilization, possibly bearing some relation to the therapeutic benefits of exercise.<sup>9</sup>

The most surprising feature pertaining to the respiratory quotients consisted in some unexpectedly high values obtained, similar to those described by Joslin. For example, Gerald S. fasted eight days, November 11 to 19, then received a gradually increasing protein-fat diet, with from 750 to 1,000 gm of thrice-boiled green vegetables daily. On the fifth day of this diet, November 23, the quotient indicated that he was deriving 2 per cent of his calories from the combustion of carbohydrate. The subsequent experiments, up to December 7, gave quo-

tients indicating combustion of between 10 and 15 per cent carbohydrate, with an average of 12 per cent. During this period the basal metabolism averaged 1,042 calories per twenty-four hours. If he were deriving 12 per cent of his calories from carbohydrate, he must have metabolized an average of 31.3 gm. a day or a total of 438 gm. in the two weeks. According to the analyses of the thrice-boiled green vegetables, which were the only possible source of starches or sugars, he could not have received more than 2 or 3 gm. of carbohydrate a day. It is improbable that he could have maintained a store of 400 gm. of glycogen in his body under the circumstances. The blood sugar did not fall enough to suggest that more than a small fraction could have been derived from this source, and the recent work of Palmer<sup>30</sup> proves, as far as is possible with animal experiments, that the quantity of sugar present as such in the tissues is insignificant. The results after the ingestion of whisky are also hard to interpret. It is known that alcohol requires a moderate amount of time, sometimes several hours, for its complete combustion, but it is impossible to tell how much alcohol is metabolized each hour, since the nonprotein respiratory quotient will not solve a problem with three unknowns. Alcohol has a quotient of 0.667, but it may possibly cause vasomotor and respiratory changes leading to an elimination or retention of carbon dioxide with resulting false quotients. But its action in normal persons or animals is to depress the quotient, in all the extensive studies concerning the utilization and effects of alcohol, a rise of the quotient after its ingestion has never been reported. In the earlier whisky experiments with Gerald S., there was a sharp rise in the quotient after drinking, followed by a corresponding fall in the second hour, the highest non-protein quotients for single hours being 0.764 on November 18, and 0.773 and 0.782 on November 20. This was not seen in control experiments in which the patient drank the same amount of plain water at the same temperature, or went through the movements of drinking without swallowing any liquid. Mild exercise, as above stated, had no immediate effect on the quotient. Finally, on Nov. 25, the whisky was given in such a way that there was absolutely no exertion on the part of the subject, and although the rise of quotient in the first hour was absent, the marked drop in the second hour was present. In this last observation there was no apparent increase in the combustion of carbohydrates, but in the first three the average quotient of the hours after whisky was slightly higher than before. There was thus an apparent increase in the carbohydrate metabolism, which would be even higher than calculated if alcohol with its low quotient were oxidized, thus tending to lower the total quotient.

Joslin has suggested that combustion of retained acetone bodies, with their high quotients (beta-oxybutyric acid 0.89, diacetic acid 1.00),

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30 Palmer, W. W. In press

may account for some rise in the quotients of these patients. The suggestion is supported by the observation that on fasting the ketonuria falls and the quotient rises. Also, if it should prove true that alcohol diminishes ketonuria, as claimed by authors<sup>31</sup> in the past, the rise of the quotient after ingestion of alcohol might correspond to an increased combustion of acetone bodies. The high quotients as described seem to be a regular or frequent phenomenon in patients with severe diabetes under the conditions described, and the possibilities may be discussed by comparison of the cases reported. The blood sugar, as stated, fell somewhat in the case of Gerald S., but rose during the development of the increased quotients in Geyelin and DuBois' patient (Cyril K.), and in the patient of Joslin.<sup>19</sup> The above calculation in the case of Gerald S. requires the equivalent of 400 gm of glycogen to explain the quotients observed. No patient could possibly retain enough acetone bodies to correspond to the whole of this requirement. The high quotients have generally been observed when the glycosuria and ketonuria were diminishing either during or after fasting, or on ingestion of whisky. An exception is present in the case of Cyril K. when receiving protein diet on December 16-17. Here the ketonuria was higher than on any previous day, namely, 75 gm reckoned as beta-oxybutyric acid. The carbon dioxide capacity of the blood plasma had fallen to its lowest point, namely, 19.6 (the normal figures being from 40 to 45). The dextrose-nitrogen ratio was at its highest point, namely, 4.01. Under these circumstances it is difficult to understand what kind of material could be burned to give the observed nonprotein respiratory quotient of 0.743. This single result may possibly be due to some accident connected with the circumstances of this particular case. On the other hand, it may possibly be of some significance in connection with the fact that, although all the laboratory tests aside from the respiratory quotient indicated that the patient was in no wise better and in some respects worse on December 16-17 than on December 9-10, yet it was evident clinically that his condition was much better on the latter date and the symptoms of intoxication greatly diminished. This patient was receiving alkali during this period, but Gerald S. and Joslin's patient received none, therefore the quotients can scarcely be due to dosage with bicarbonate. It is conceivable that high quotients in one part of the twenty-four hours might be compensated by low quotients in another part. No respiration experiments were performed at night, but it is scarcely probable that any marked difference existed between

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31 Neubauer, O. Ueber die Wirkung des Alkohols auf die Ausscheidung der Azetonkörper, München med. Wchnschr., 1906, lxxi, 791. Benedict, H., and Torok, B. Der Alkohol in der Ernährung der Zuckerkranken, Ztschr. f. klin. Med., 1906, lx, 328. Staubli, C. Beiträge zur Pathologie und Therapie des Diabetes mellitus, Deutsch. Arch. f. klin. Med., 1908, xciii, 107.

day and night. Such a difference would in itself constitute an abnormality, for the day and night quotients have never been known to vary to such an extent in previous experiments on normal persons and animals. It is noteworthy that while the average divergence between the methods of direct and indirect calorimetry in the present series was only 2.3 per cent, and the agreement was close in the first experiments with Gerald S., yet beginning with the eighth day of his fast, November 18, when the period of high quotients began, there appeared minus errors of the direct as compared with the indirect calorimetry sometimes as high as 21, 14 and 16 per cent. Such discrepancies might in part be explained if the quotients were due to combustion of some other material, perhaps acetone bodies, instead of carbohydrate as assumed, for then the reckoning of the indirect calorimetry would be considerably altered. On the other hand the divergence may possibly have been due to technical error in the measurement of the average temperature of the body.

4 *The Total Metabolism*—In regard to the general question of heat production the present series of experiments agrees with the work of previous authors in showing the basal metabolism per kilogram of body weight to be increased in severe diabetes. But as above mentioned, the principal need in connection with this vexed question has been a satisfactory standard of comparison between diabetic and non-diabetic subjects. The linear formula devised especially to throw light on this subject is believed to afford such a standard, and the conclusions in the present paper are drawn on the basis of this mode of calculation. The summary in Table 8 shows that the surface area of thin diabetics is not so much smaller than that of normal men as would be indicated by Meeh's formula, and consequently their metabolism is considerably lower when compared with the normal average according to the linear or height-weight formula than when Meeh's less accurate formula is used. The difference between the results as expressed in terms of the two formulas in the case of Gerald S. is from 8 to 13 per cent. With William G. it is from 11 to 18 per cent, with Joseph U., 10 per cent, with John O'C., from 11 to 12 per cent. These were all very thin diabetics, and the differences with less emaciated patients would be proportionately smaller. With patients stouter than the average the metabolism would be higher according to the linear formula than according to Meeh's, but patients with severe diabetes are seldom stout.

Among the patients described in the present paper, it was noted that Gerald S. entered the hospital in a weak and exhausted condition. His metabolism at this time, November 9, was 2 per cent above the average normal by Meeh's formula, but 8 per cent below the average normal by the linear formula. William G. had been subjected to

prolonged low diet. Starting at 26 per cent below normal on January 11, when glycosuria was absent, his metabolism rose, on increased diet and the return of active diabetes, to 20 per cent below normal on January 15 and to 11 per cent below normal on January 22. On the other hand, in the patient of Geyelin and DuBois<sup>26</sup> (Cyril K.), the diabetes was recent and acute, and here the metabolism was above normal. The respiration experiment on December 15 was after food, therefore the metabolism of 15 per cent above normal does not represent a true basal value. The highest basal metabolism actually demonstrated here was 3 per cent above normal on December 18.

The patient Edward M. never showed the true ravenous hunger of diabetics, but had been a heavy eater all his life and could dispose of a large diet exceptionally well, with no increase of his slight dyspeptic complaints. During most of September, weighing 58 to 63 kg and leading the inactive life of a ward patient, he had enjoyed a high diet, the maximum being during the period September 21 to 26, with from 6,100 to 6,300 calories daily, consisting chiefly of fat, of which there was nearly 600 gm daily. Instead of steatorrhea, there were small constipated stools, showing exceptionally high utilization by analysis. As stated in his history, the diet had been moderate but adequate preceding the first calorimeter tests. The body weight was about 60 kg, as opposed to his original "normal" weight of about 80 kg. But he felt well and strong at this weight, and, correspondingly, the basal metabolism on October 30 was found entirely normal, 3 per cent below the average. On October 31 the metabolism was measured two to five hours after drinking 97 gm olive oil. Table 8 shows the resulting increase of metabolism and lowering of the respiratory quotient. On November 3 the diet contained 5,300 calories with 483 gm fat, and on November 4, 5,268 calories with 482 gm fat. On the morning of November 5 the patient entered the calorimeter after taking 44 gm protein, 38 gm carbohydrate and 204 gm fat. The metabolism two to five hours afterward is shown by Table 8 to average 17 per cent above normal. Accordingly, the specific dynamic action of food, especially of fat, did not differ noticeably from the normal as respects its promptness or intensity in this patient, and there was no indication of an abnormally high metabolism ("Luxuskonsumption") on the excessive diet. The result with this patient under the conditions does not warrant a positive conclusion concerning possibilities in more severe cases, especially at the height of the diabetic process.

Since the last important discussion of the total metabolism in diabetes by Benedict and Joslin there have been several changes in the general point of view of the metabolism of normal controls and of diabetics as the result of work presented in previous papers of this series. In the light of these it has seemed advisable to recalculate the

cases of severe diabetes reported in the literature, and discuss the question in its most recent aspects. As we have shown, it is advisable to abandon comparisons made on the basis of cubic centimeters of oxygen per kilogram and minute and use instead the calories per square meter per hour. Recent work on the metabolism at different ages has emphasized the fact, first brought out clearly by Magnus-Levy and Falk,<sup>32</sup> that metabolism changes with age. It must be remembered that a study of the surface area designed primarily to afford a basis of comparison between patients and normal controls has shown that Meeh's formula is not so accurate as the newly devised linear and height-weight formulas. Most important of all has been the study of a large number of controls by Benedict, by Means<sup>33</sup> and by the Russell Sage Institute staff, giving a normal basis of comparison which is not influenced by variations that might occur in small groups or by single investigators.

In Table 9 are given the results obtained in a large number of cases of severe diabetes. Since the height-weight formula was employed as a basis of comparison, the only cases that could be used were those where the height was given. This unfortunately has prevented the recalculation of the severe cases of Leo,<sup>34</sup> Nehring and Schmoll,<sup>35</sup> Rolly,<sup>36</sup> and some of the cases of Magnus-Levy<sup>34</sup> and Mohr.<sup>36</sup> The work of Leindorfer<sup>37</sup> has not been recalculated, since the abnormally low quotients make this impossible, nor has the work of Grafe and Wolf,<sup>37</sup> where it is difficult to reconcile the high respiratory quotients and high dextrose-nitrogen ratios. As will be seen, the large majority of cases was furnished by the careful work of Benedict and Joslin. For purposes of comparison, columns have been added showing the duration of life after the period of experimentation, the level of the nitrogen metabolism, the degree of emaciation, and the estimated degree of acidosis. If we study first the column showing the percentage variation from the normal, it will be noted that out of twenty-six cases thirteen are within the normal range of plus or minus 10 per cent from the average. There are nine patients with an increase

32 Magnus-Levy, A., and Falk, E. Der Lungengaswechsel des Menschen in den verschiedenen Altersstufen, *Arch f. Physiol*, 1899, Suppl., 314.

33 Means, J. H. Basal Metabolism and Body Surface, *Jour. Biol. Chem.*, 1915, *xxi*, 263.

34 Leo, H. Ueber den respiratorischen Stoffwechsel bei Diabetes mellitus, *Ztschr. f. klin. Med.*, 1891, *xix*, Suppl., 101.

35 Nehring, O., and Schmoll, E. Ueber den Einfluss der Kohlehydrate auf den Gaswechsel des Diabetikers, *Ztschr. f. klin. Med.*, 1897, *xxvi*, 59.

36 Mohr, L. Untersuchungen über den Diabetes mellitus, *Ztschr. exp. Path. u. Ther.*, 1907, *iv*, 910.

37 Grafe, E., and Wolf, G. L. Beiträge zur Pathologie und Therapie der schwersten Diabetesfälle, *Arch. f. klin. Med.*, 1912, *cxvii*, 201.

of from 11 to 23 per cent and these deserve special attention. Two of these, V and Cyril K, were studied after food, and if the stimulus of the recent meal were removed they might have come within normal limits. One of the subjects, G, was under intense nervous excitement during the experiment, and another, I, with a pulse of 120, had been described the year before as very nervous. This leaves us five cases in which there was a moderate but distinct rise in the metabolism, namely, Herr Mo, Frau Schm, Frau St, H, and U. To these we should perhaps add Cyril K at the time of his first experiment, when after a breakfast his metabolism was 15 per cent above the normal basal. To offset these there are four patients whose metabolism ranged from 14 to 19 per cent below the average. Three of these, N, P and Q, were children, and it is quite possible that the normal stimulus of the growing organism was checked by the diabetes. The fourth subject, Wm G, was extremely emaciated. If we take the algebraic mean of the 26, we find that the metabolism in severe diabetes averages 3.3 per cent above the normal, a figure which might be increased to about 5 per cent by taking into account the fact that the average for the 89 normal controls of Benedict is 2 per cent lower than the Sage standards.

Benedict and Joslin<sup>4</sup> found that the average oxygen consumption of their diabetics per kilogram and minute was 15 to 20 per cent above that of their twenty normal controls. Part of this difference was due to the fact that at that time few investigators realized the importance of the age factor. Part was due to the unusually low metabolism of the normal controls. In the twenty controls used by Benedict and Joslin for comparison with the diabetics, there are seven whose metabolism is 10 per cent or more below the average normal described in the previous papers of this series. It so happens that these seven, A, F, G, T, M, C, Dr P, R, Dr S, H, F, T, E, P, C, Mrs S, C, are used seventeen times in the total column of thirty-two, making the average of the column 8.6 per cent below the standard. This is much greater than the divergence of —2 per cent found in the total of eighty-nine normal controls. Their cases with severe diabetes, recalculated in terms of the height-weight formula, average only two per cent above the Sage normal standard. It would appear that the metabolism of Benedict and Joslin's diabetic patients is within normal limits, while the large difference between their pathologic and normal cases is due chiefly to the low metabolism of the subjects selected for normal controls. It is quite possible that the low metabolism of these controls was due to the fact that they were poorly nourished and were selected because they resembled diabetics in this respect.



TABLE 9—THE BASAL METABOLISM OF PATIENTS WITH SEVERE  
SURFACE AREA AS ESTIMATED BY

Investigator	Subject	Sex	Age Yrs	Calories per Sq. M. per Hr. Height Weight Chart	Normal Stand- ard Cal per Sq. M. per Hr. for Same Age and Sex	Per Cent Varia- tion from Normal Stand- ard	Respir- atory Quo- tient, Average
Magnus Levy	Herr Mo	♂	43	49.9	39.7	+18	0.70
	Frau Schm	♀	35	41.2	36.9	+11	0.72
Mohr	Frau St	♀	2	40.5	32.7	+23	0.71
Perdick and Joslin	A	♂	50	46	39.2	+4	0.71
	B	♀	40	36.0	36.9	-2	0.73
	C	♂	25	40.1	39.7	-1	0.70
	D	♂	39	36.9	39.7	-7	0.74
	G	♂	35	45.1	39.7	+14	0.73
	H	♀	38	40.9	36.9	+11	0.77
	I	♂	25	45.2	39.7	+14	0.73
	J	♂	20	43.6	39.7	+10	0.76
	K	♂	46	39.1	39.7	-2	0.72
	L	♂	23	43.5	39.7	+10	0.75
	N	♂	14	43.0	49.9	-14	0.74
	O	♀	16	37.9	39.0	-3	0.72
	P	♂	15	39.7	49.0	-19	0.69
	Q	♂	14	42.2	49.0	-15	0.77
	R	♂	47	48.6	39.7	+10	0.72
	S	♂	37	31.2	35.2	-3	0.73
	T	♂	44	39.6	39.7	0	0.73
	U	♀	37	42.1	36.9	+15	0.73
	V	♂	36	45.8	39.7	+15†	0.73
Geyelin and DuBois	Cyril K. Dec 15 & 16	♂	21	44.2	39.7	+11†	0.70
	Dec 18	♂	21	40.8	39.7	+3	0.71
Authors	Gerald S. Nov 9 & 12	♂	17	39.7	39.7§ (42.0*)	-5 (-10*)	0.71
	William G. Jan 15 to 22	♂	29	33.7	39.7	-15	0.70

\* Using average normal for age of 17

† Part of increase due to recent food

§ Using average normal for ages 20 to 50

DIABETES COMPARED WITH NORMAL STANDARDS ACCORDING TO THE  
THE "HEIGHT-WEIGHT" FORMULA

Time Before Death in Months		Urine N per Day, Gm	Emaciation or Per Cent of Loss from Greatest Weight	Degree of Acidosis	Remarks B = Beta oxybutyric Acid per Day
Coma	2		++	++?	
Coma	6		++	++?	
				±	Moderately severe, Diac 0 to +
Tb	20	6 14	Per Ct 10 18	+	NH <sub>3</sub> N 3 3, Diac +, Active Tb in lungs
Coma	6 1		9 18	++(?)	Diac +++++
Coma	2	13 22	14 24	+++	B 14 to 61, NH <sub>3</sub> N 2 6 to 5 6
Coma	3	13	15	0 +	Diac 0 to +++++, urine alk with 8 to 45 sod bicarb
Coma	15	17	+	+++	B 30, NH <sub>3</sub> N 4 2, Diac +++++, intense nervous excitement during experiment
Coma	4	9 12	14	+	B 8 to 11, Diac 0 to +
	15	14	30	±	B 4 8, NH <sub>3</sub> N 2 2, pulse 120 (nervous?)
	36		15	±	Diac + to ++, nervous temperament
Coma	16 4	16 20	20 24	0 ++	B 30, Diac 0 to ++, NH <sub>3</sub> N 3 to 5 8
Alive			20 16	±	Diac 0 to sl +
Coma	1½	5 10	9	+++	B 21 to 30, Alv CO <sub>2</sub> Hald 16 to 28
Coma	3	8 11	14	+	B 13 to 14
Coma	1	5 18	20	+++	Diac +++++, NH <sub>3</sub> N 4 6 to 5
Coma	4	7 14	5	++	B 20 to 27, NH <sub>3</sub> N 2 2 to 4 6, Alv CO <sub>2</sub> 31 to 40
Tb	10	13 16	17	++	B 42 to 50, NH <sub>3</sub> N 5 to 6, somewhat nervous, moved considerably
Coma	5	7 3	18	+	Diac ++, NH <sub>3</sub> N 1 2
Coma	1	9 12	28	+++	B 40 to 50, NH <sub>3</sub> N 4 6 to 5 2, Boils
Coma	15 3	7 9 5	26	++	B 18 to 22, NH <sub>3</sub> N 3 6 to 4
Pneu	11		6	0	Diac 0 After light breakfast
Alive		36 37	27	+++	B 71 to 75, blood CO <sub>2</sub> 19 6 to 20
Alive		20	27	+++	After large breakfast B 58, blood CO <sub>2</sub> 35, second fast day
Coma	4	11 15	31	++	B 3 to 14, NH <sub>3</sub> N 3 4 to 4 7
Coma Tb	2	14 20	42	+	
					Diac ++, NH <sub>3</sub> N 3 4, B 0 1 to 1 3

TABLE 10—METABOLISM EXPERIMENT ON MAGNUS-LEVY'S PATIENT\*

Period	Date	Condition	Calories per Sq M per Hour Height- Weight Formula	Weight, kg	Relation ship of Metabolism to Average Normal 39.7
I	Nov 16 to 21	Very low diet	26.6	36.2	-33%
II	Nov 23 to Dec 9	Liberal diet	33.0	38.0	-17%
III	Jan 26 to March 6	Fever from T.b	43.4	48.4	+ 9%
IV	March 13 to May 8	Normal again	40.7	52.2	+ 2%

\* Age 19, height 160 cm

These figures are comparable to those shown in the present series of diabetic patients after treatment. The degree of elevation of metabolism due to the active diabetic process should be judged by comparison of such patients with equally emaciated and cachectic nondiabetics. It is also now possible to compare the same patient at times when active diabetes is present or absent, while the body weight and surface remain the same. Thus Gerald S., with intense diabetes, on November 9 had a basal metabolism 8 per cent below normal. His fast ended November 18, and from then until December 7 he received a diet such that his

38 Recalculated in terms of surface area according to Meeh's formula, by Coleman and Du Bois, The Influence of the High Calory Diet on the Respiratory Exchanges in Typhoid Fever, THE ARCHIVES INT MED, 1914, XIV, 168 (Fig 4)

39 Magnus-Levy, A. Der Einfluss von Krankheiten auf den Energiehaushalt in Ruhezustand, Ztschr f klin Med, 1906, lx, 177

weight on the latter date was practically identical with that on November 9, but the basal metabolism on December 7 was 22 per cent below normal at a time when the urine was free from sugar. William G weighed 43.2 kg on December 11. In consequence of feeding high-caloric diet, the weight fell to 42 kg by December 22, while the metabolism rose from 26 per cent below normal on December 11 to 11 per cent below normal on December 22. If we study Table 9 it is apparent that most of the diabetics with marked emaciation have a diminution in metabolism. In the children with diabetes and low metabolism the percentage loss from the greatest weight is small, but with a child that is growing taller even a stationary weight indicates emaciation. If "normal" adults and children were as emaciated as the diabetics, they would undoubtedly show a marked diminution in heat production.

Benedict and Joslin have ascribed an increase in diabetes to acidosis. This is usually associated with an increased protein metabolism, and it is often difficult to separate the two factors. It has long been known that increased protein metabolism causes an increased heat production. If we turn to Table 9 we can compare the increased metabolism with the degree of acidosis. There were nine patients whose metabolism was 11 to 23 per cent above the normal. Of these two showed marked acidosis, namely, Cyril K and the nervous patient G. Three others, Herr Mo, Frau Schm and U, had severe acidosis. Patient H had moderate acidosis, while the others, I and V, had little or no acidosis, and the patient Frau St, with the highest metabolism of all, had very slight acidosis. In contrast to this, eight patients with severe or very severe acidosis showed a normal or decreased metabolism. These are B, C, N, P, Q, T, Cyril K (December 18), and Gerald S.

Authors have erroneously attempted a direct comparison between dogs depancreatized or phlorhizinized at the height of their strength, and human patients who reach the stage of severe diabetes, generally after months of a slow cachexia. Accurate comparison demands equally acute human diabetes, or else the use of dogs with chronic diabetes or prolonged cachexia. The excessive nitrogen excretion of William G and especially of Cyril K (Geyelin and DuBois) is well comparable to that of the totally depancreatized dog, and in the latter the total metabolism was actually above normal in spite of four weeks of rapid wasting followed by five days of complete fasting. The alleged difference as respects increase of metabolism can therefore no longer stand as a distinction between clinical and experimental diabetes.

Theoretically it is to be expected that the metabolism will rise with the increase of the protein metabolism which accompanies the noncombustion of sugar derived from protein in the diabetic condition. Since the specific dynamic action is less in human beings than in dogs, it may

well be that the stimulus of an increased protein metabolism is relatively less pronounced in human than in experimental canine diabetes.

Recapitulating one may state that the linear formula furnishes a more accurate standard of comparison than was previously available.

According to calculation by this formula, an increase above the true normal metabolism is not demonstrable in the majority of patients with severe diabetes. Nevertheless, the diabetic process may be associated with a relative elevation of metabolism. In occasional instances the metabolism may actually exceed the average normal level of metabolism. In all cases the true increase appears only when one takes into consideration other factors incidentally present, some of them tending strongly to depress metabolism. For example, the percentage of increase may be fully as great as claimed by Benedict and Joslin, if the metabolism of diabetics is compared with that of other equally undernourished subjects, or if the same patient is compared at different times when active diabetes is present or absent. In practical application, the results indicate that diabetics generally have no higher food requirement than normal, and on account of undernutrition and lessened muscular activity will tend to maintain equilibrium on a smaller number of utilizable calories than normal persons. Because the diabetic is less active, as pointed out by Magnus-Levy, his actual consumption of energy as compared with normal controls is likely to be less. After treatment by fasting, even though the patient is gaining steadily in strength and well-being, a low level of metabolism has been observed, the lowest 36 per cent below normal, and this indicates that a low diet will suffice for maintenance under these conditions.

#### SUMMARY AND CONCLUSIONS

1 Three patients with severe diabetes and three with moderate or mild diabetes have been studied in the respiration calorimeter. The effects of the oatmeal treatment and the fasting treatment have been followed in detail.

2 No special influence of oatmeal in diabetes on special readiness of oxidation of this form of carbohydrate was demonstrable in these experiments. The respiratory exchange fails to account for all the carbohydrate that disappears. The behavior of the respiratory quotient showed no important difference on the first day and on the third day of the oatmeal treatment.

3 The occurrence of "total" diabetes in human patients, with dextrose-nitrogen ratios approximating 3.65 to 1 and corresponding respiratory quotients is here shown. Notwithstanding the extreme severity, neither the sugar excretion nor the gaseous exchange gives ground for assuming the formation of sugar from fat in any instance.

4 Even in the severest type of diabetes the active symptoms may

be eliminated completely by prolonged fasting. The observations in the respiration calorimeter prove that patients as a result of the fasting acquire the power of oxidizing sugar derived first from their own body protein and later from the protein and carbohydrate of a carefully regulated diet.

5 The respiratory quotients during fasting and after the glycosuria had ceased were in some such instances higher than can be easily explained by the oxidation of the materials supposedly available. Also the ingestion of alcohol was sometimes followed by respiratory quotients higher than would theoretically be expected. The data will be analyzed in a subsequent paper.

6 The specific dynamic action of food, especially fat, was apparently normal in a patient with moderately severe diabetes.

7 The results of two respiration experiments in a severely diabetic patient have shown that mild exercise slightly raises the quotient, and this suggests the possibility that exercise may improve carbohydrate utilization. Generalizations or positive conclusions from these experiments are not attempted.

8 According to comparisons of the surface area as calculated by the linear formula, increase of the basal metabolism above the true normal level in severe diabetes is generally absent or slight. The metabolism was shown to fall markedly during fasting, to 20 per cent below normal. The level of metabolism in diabetes is the resultant of a number of forces, for example, increased destruction of protein and perhaps other processes tending to increase metabolism, and undernutrition, muscular relaxation (as in prolonged confinement in bed) and other possible conditions tending to diminish metabolism. According as one or the other of these groups of forces predominate, a higher or lower metabolism may be expected in any individual case of diabetes.



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